Epidemiology of Ischaemic Stroke Subtypes

Do Differences in Epidemiology Provide Evidence for a Distinct Lacunar Arterial Pathology?

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Declaration

I hereby declare that I composed this thesis, and that the content is my own, original work. The data presented in my thesis has not previously been submitted for examination for any other degree, postgraduate diploma or professional qualification. The idea for the Edinburgh Stroke Study (ESS) was conceived by the Principal Investigator Dr Cathie Sudlow (CLMS). The study was designed by CLMS, with input from Professors Martin Dennis and Joanna Wardlaw, and myself. I was the study co-ordinator, responsible for co-ordinating patient recruitment and baseline data collection by clinicians, data entry and follow-up of patients. Aidan Hutchison (AH) developed the database, and carried out data programming and formatting, under my guidance and direction. I performed further data manipulation, and planned, carried out and interpreted all statistical analyses of data. Brenda Thomas and CLMS created the Medline literature search strategy for the systematic reviews, which I adapted for use in Embase. CLMS acted as a second reviewer, carrying out duplicate extraction of data. Laura Crossland (medical student) helped with investigating the effect of the requirement for consent in the Edinburgh Stroke Study. CLMS developed the collaborative links with the Principal Investigators of the stroke registers included in my pooled individual patient data analyses. She sought and obtained the individual patient data and performed initial data checks, with programming support from AH. AH also carried out the computer programming for the combined stroke register database. I completed the data checks, and planned, carried out and interpreted statistical analyses of the pooled data.

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Publications associated with the work presented in this thesis

Jackson C, Hutchison A, Dennis MS, Wardlaw J, Lewis S, Sudlow CLM. Differences between ischaemic stroke subtypes in recurrent stroke and myocardial infarction support a distinct lacunar ischaemic stroke arteriopathy: a prospective, hospital-based study *(submitted to Lancet Neurology)*

Jackson CA, Hutchison A, Dennis MS, Wardlaw JM, Lindgren A, Norrving B, Anderson CS, Hankey GJ, Jamrozik K, Broadhurst RJ, Appelros P, Sudlow CLM. Risk factors for lacunar versus non-lacunar ischaemic stroke: a collaborative individual patient data analysis *(submitted to Annals of Neurology)*

Jackson C, Crossland L, Dennis M, Wardlaw J, Sudlow C. Assessing the impact of the requirement for consent in a hospital-based stroke study. *QJM* 2008; 101: 281-289.

Jackson C, Sudlow C. Comparing risks of death and recurrent vascular events between lacunar and non-lacunar infarction. *Brain* 2005; 128: 2507-2517.

Jackson C, Sudlow C. Are lacunar strokes really different? - a systematic review of differences in risk factor profiles between lacunar and non-lacunar infarcts. *Stroke* 2005; 36: 891-904

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I dedicate this thesis to my brother Fraser,
and to my parents, John and Dianne

Abbreviations

AF	Atrial fibrillation
CI	Confidence interval
CS	Carotid stenosis
CT	Computed Tomography
DW MRI	Diffusion weighted magnetic resonance imaging
ESS	Edinburgh Stroke Study
ECG	Electrocardiogram
ECHO	Echocardiogram
GP	General Practitioner
HR	Hazard ratio
ICA	Internal carotid artery
IHD	Ischaemic heart disease
LACI	Lacunar ischaemic stroke
LACS	Lacunar syndrome
MI	Myocardial infarction
MR	Magnetic resonance
OCSP	Oxfordshire Community Stroke Project
OR	Odds ratio
PACI	Partial anterior circulation infarction
PAD	Peripheral arterial disease
PACS	Partial anterior circulation syndrome
POCI	Posterior circulation infarction

POCS	Posterior circulation syndrome
RR	Relative risk (or risk ratio)
TACI	Total anterior circulation infarction
TACS	Total anterior circulation syndrome
TIA	Transient ischaemic attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment

Abstract

Background Lacunar ischaemic stroke accounts for around one quarter of all strokes, and is presumed to result from the occlusion of a single perforating artery supplying the deep subcortical areas of the brain. The underlying arterial pathology is poorly understood, but is thought to differ from the atherothrombotic processes that occlude larger intra- and extracranial arteries causing most other ischaemic stroke subtypes. Progress in understanding the aetiology of lacunar stroke has been limited by the lack of informative autopsy studies, and the difficulties in studying small blood vessels using brain imaging. One alternative approach is to compare the epidemiology of ischaemic stroke subtypes, since differences in the epidemiology may reflect and inform about different underlying pathologies.

Methods I performed two systematic literature reviews to identify studies presenting data on (1) the risk factors for, and (2) the outcome of, different ischaemic stroke subtypes. I extracted relevant data from included studies and performed a series of meta-analyses comparing risk factor profiles, and risks of death, recurrent stroke and myocardial infarction (MI) in patients with lacunar versus non-lacunar ischaemic stroke. To address some of the unanswered questions and controversies surrounding the causes of ischaemic stroke we set up the Edinburgh Stroke Study (ESS), which I co-ordinated. We recruited patients with stroke and transient ischaemic attack seen at our hospital between 2002 and 2005, and followed them for 1-4 years for death, recurrent stroke and MI. To overcome the methodological limitations of the studies included in my reviews and of my meta-analyses, I carried out a large collaborative individual patient data analysis in which I combined data from five stroke registries - including the ESS - that had used similar robust methodology, and performed a series

of analyses comparing the risk factor profiles of patients with lacunar versus non-lacunar ischaemic stroke. In an updated meta-analysis, I combined this data with existing published studies that had used an unbiased method of classifying ischaemic stroke subtypes. Using the ESS data, I compared the risks of recurrent stroke and MI, and patterns of recurrent stroke subtypes in patients with lacunar versus non-lacunar stroke.

Results In my systematic review of risk factors I found evidence of classification bias in many studies, where systematic error was introduced through the use of classification methods that included risk factors in the definitions of stroke subtypes. This led to overestimation of some risk factor-stroke subtype associations and, in particular, to apparently stronger associations between hypertension and diabetes and lacunar compared with non-lacunar ischaemic stroke. When I included only unbiased studies, I found a significantly reduced prevalence of atrial fibrillation (AF) and severe carotid stenosis and a trend towards a reduced prevalence of ischaemic heart disease (IHD) in lacunar patients. I found a very slight excess of hypertension among lacunar patients, but no difference in the prevalence of diabetes, or any other risk factor studied. In my collaborative individual patient data analysis, I confirmed a significantly lower prevalence of severe carotid stenosis, AF and previous IHD in patients with lacunar ischaemic stroke, but found no difference in the prevalence of hypertension, diabetes, or any other risk factor studied, even after adjusting for confounding factors. These results were largely confirmed in my updated meta-analysis, although there was a slight excess of hypertension among lacunar compared with non-lacunar ischaemic strokes. In my systematic review of outcome after lacunar versus non-lacunar ischaemic stroke, I found a lower risk of death following

lacunar compared with non-lacunar stroke which attenuated but persisted long-term; a higher recurrent stroke risk in non-lacunar patients during the first month only; and limited data on recurrent stroke subtypes suggesting that ischaemic stroke subtypes may breed true to type. Data on MI risk were extremely sparse. My analyses of data from the ESS showed no difference overall in risk of recurrent stroke between patients with lacunar versus non-lacunar ischaemic stroke, but some evidence for a lower very early recurrence risk among lacunar patients. There was evidence that recurrent stroke subtypes breed true, since patients with a lacunar stroke at baseline were much more likely to have a lacunar than a non-lacunar recurrence. We identified five times as many MI events following stroke than have been previously reported in the published literature, and found a non-significantly reduced risk of MI in patients with lacunar compared with non-lacunar ischaemic stroke.

Conclusions My comparisons of the epidemiology of lacunar versus non-lacunar ischaemic stroke subtypes revealed differences in the risk factor profiles and risks of recurrent stroke and myocardial infarction which suggest that a distinct, non-atherothrombotic arteriopathy underlies many lacunar ischaemic strokes. My analyses of recurrent stroke subtype patterns suggest that recurrent ischaemic strokes subtypes tend to breed true, providing further support for a distinct lacunar arteriopathy. Contrary to widespread belief, hypertension and diabetes do not appear to be more important in the aetiology of lacunar stroke than in other types of ischaemic stroke.

These findings support other lines of evidence for a distinct lacunar arteriopathy, and highlight the need for further research into the aetiology of lacunar ischaemic stroke.

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1.1 Global impact of stroke

1.1.1 Mortality

Stroke, defined by the World Health Organisation as the clinical syndrome of rapid onset of focal cerebral deficit, lasting more than 24 hours or leading to death and with no apparent cause other than a vascular one (Aho *et al*. 1990), is a major public health burden. It is the third most common cause of death worldwide, second to ischaemic heart disease and all cancers combined, and the second commonest cause of death when cancer is divided into its different types (Lopez *et al*. 2006). Stroke is becoming a major health problem in middle- and low-income countries, where there has been a 50% increase in the burden of chronic diseases in the last decade (Strong *et al*. 2007). In 2005, stroke caused an estimated 5.7 million deaths worldwide, 87% of which occurred in low- and middle-income countries (Strong *et al*. 2007).

1.1.2 Incidence

Stroke is largely a disease affecting older people, with the incidence risk increasing with each decade of life and three-quarters of all first strokes occurring after the age of 65 years (Feigin *et al*. 2003). Most methodologically robust incidence studies have been performed in predominantly Caucasian populations in Europe, Australasia and the USA. Among population-based incidence studies carried out since 1990, the

age-adjusted incidence of total stroke for those aged more than 55 years ranged from about 4.2 to 11.7 per 1000 person-years (Feigin *et al*. 2003).

Incidence data from the UK is in keeping with data from other high-income countries, with a handful of community-based incidence studies carried out in England after 1990 having reported age-standardised incidence rates for all stroke types that range from 1.3 to 1.6 per 1000 per year (Du *et al*. 1997; Rothwell *et al*. 2004; Stewart *et al*. 1999). For ischaemic stroke in particular, the most recent incidence study reported an age-standardised incidence rate of 1.4 per 1000 per year (Rothwell *et al*. 2004). Similarly, the only study to have accurately measured stroke incidence within Scotland – the Scottish Borders Study – recently reported an age-standardised ischaemic stroke incidence rate of 1.6 per 1000 per year (Syme *et al*. 2005). It is difficult to compare these two most recent stroke incidence studies in Scotland and England since different reference populations were used in the age standardisation. There are, however, almost no reliable incidence data from low- and middle-income countries.

1.1.3 Trends and projections

Most studies have shown an overall decline in stroke incidence, particularly in the elderly population, in Western Europe, Australasia, Japan and the USA through the 1970s and 1980s, with incidence generally stabilising in the 1990s. Elsewhere, stroke incidence has risen in some Eastern European countries (Feigin *et al*. 2003, Truelsen *et al*. 2006).

Routinely collected data suggest that mortality rates have similarly declined in many countries since the mid 1960s, particularly in Western Europe, North America, Australia and Japan (Sarti *et al*. 2000), but may have stabilised over the last ten

years. However, with increasing life expectancy, the global population aged over 65 years is increasing by 9 million per year, and the projections are that by 2025 there will be over 800 million people aged over 65 years in the world (Truelsen *et al* 2001). Despite stabilising incidence rates in many countries, these demographic changes will lead to a substantial increase in the number of stroke events, with the rate of death from stroke for all ages combined estimated to increase from 89 per 100,000 in 2005 to 98 per 100,000 in 2030 (Strong *et al*. 2007).

1.1.4 Disability

Not only is stroke one of the leading causes of death worldwide, it is also responsible for a substantial proportion of the world's disability burden. Following a stroke, about one third of patients will die within a year, and of those who survive, almost half remain dependent (Warlow *et al*. 2003). There are about 250,000 disabled stroke survivors in the UK alone (Rothwell 2001). In 2001, stroke caused 4.5% of the total disability burden among low- and middle-income countries, and 3.6% of the disability burden among high-income countries (Lopez *et al* 2006).

1.1.5 Economic burden

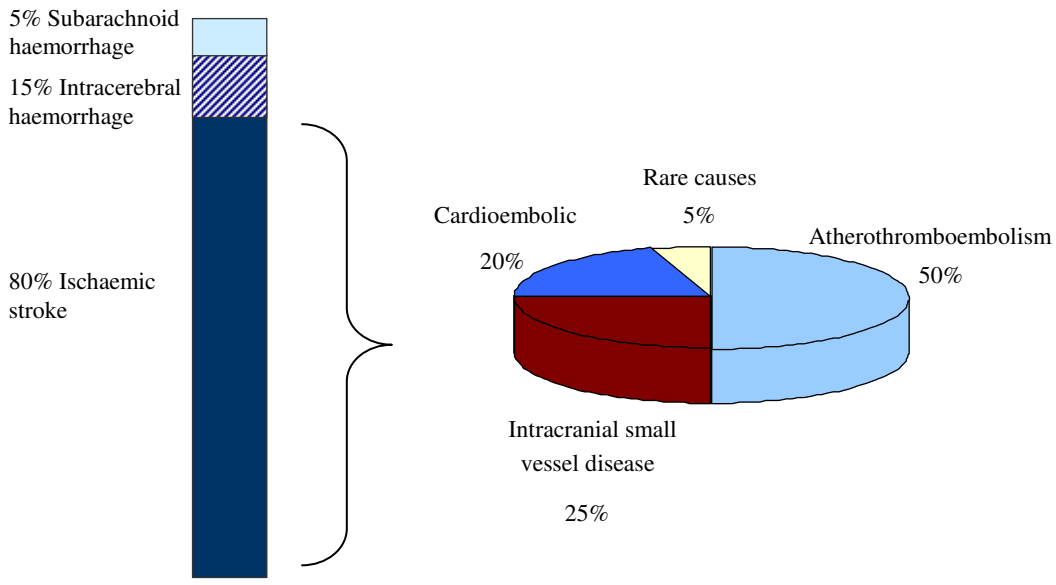
Stroke is a major drain on health-care funding, through the costs of treatment, hospital care and the huge disability burden. In the UK stroke accounts for about 6% of the National Health Service and Social Service expenditure, which equates to about £2.3 billion per year (Rothwell 2001).

1.2 Pathological types and subtypes of stroke

Stroke is a heterogeneous disorder: about 80% are ischaemic, resulting from occlusion of one or more arteries; 15% are caused by intracerebral haemorrhage, (bleeding within the brain tissue); and 5% are due to subarachnoid haemorrhage

(bleeding into the subarachnoid space – the area between the arachnoid and the pia mater) (Figure 1.1). Ischaemic stroke can be sub-classified further: among Caucasian populations about 50% are due to atherothrombosis of the extracranial arteries, and - less commonly - of the intracranial arteries; 20% are due to emboli from the heart; 25% are lacunar strokes, presumed to be caused by an intrinsic small vessel disease; and the remainder are due to rare causes such as arterial dissection and monogenic disorders (Warlow *et al*. 2003). There do appear to be ethnic differences in the incidence of ischaemic stroke subtypes, with the incidence of lacunar ischaemic stroke perhaps higher among Asian, Black and Hispanic populations compared with Caucasian populations (Feigin *et al*. 2006; White *et al*. 2005).

Figure 1.1 Estimates of the frequency of the pathological types and subtypes of stroke in Caucasian populations



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1.3 Classification of ischaemic stroke subtypes

Correct diagnosis of stroke and its pathological types and subtypes is based on a patient's clinical signs and symptoms, usually (but not always) accompanied by brain imaging findings. A diagnosis of stroke versus not stroke is primarily made based on clinical symptoms and signs, with brain imaging findings used to rule out occasional non-stroke diagnosis (e.g. brain tumour). Assignment of pathological type of stroke requires appropriately timed brain imaging to correctly distinguish between ischaemic and haemorrhagic stroke. Once a stroke is diagnosed as being ischaemic, a specific ischaemic stroke subtype can then be assigned, using one of a number of methods, as described below. Although brain imaging may visualise an acute infarct which can help in assigning an ischaemic stroke subtype, brain imaging is normal (i.e. there is no visible relevant lesion) in up to about one third of patients with a clinical stroke (Mead *et al*. 2000), although this proportion varies depending on type and timing of brain scan. An infarct may not be visible because the scan is performed too soon after stroke onset or the lesion is too small to be visualised.
In epidemiological studies, and in clinical practice, ischaemic stroke subtypes are generally assigned using one of two main classification methods: the Oxfordshire Community Stroke Projection (OCSP) classification (Bamford *et al*. 1991) or the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification (Adams *et al*. 1993).

1.3.1 Oxfordshire Community Stroke Project classification

The OCSP classification defines ischaemic stroke subtypes according to the arterial territory of the brain that is affected, and the likely size of the stroke lesion, with the four clinical syndromes being: total anterior circulation stroke (TACS); partial

anterior circulation stroke; (PACS); lacunar stroke (LACS) and posterior circulation stroke (POCS). This classification therefore relies on the clinical presentation, with the assigned clinical syndrome based on the patients' symptoms and signs, which reflect the territory of brain affected (Appendix 1). The OCSP classification predicts early death, long-term disability and recurrent stroke (Bamford *et al*. 1991), and relates to the presumed pattern of vascular pathology of each subtype (Wardlaw *et al*. 1996). The inter-observer reliability of the clinical OCSP classification was moderate to good when assessed in a hospital-based setting by neurologists (Lindley *et al*. 1993) and in a community-based setting by both neurologists and trained research nurses (Dewey *et al*. 2001). In both studies poor inter-observer agreement was related to differences in the neurological signs elicited by the observers, particularly the assessment of speech dysfunction and the presence or absence of hemianopia (visual field defect). All or some of a patient's neurological symptoms may have resolved by the time a clinical assessment is made by a doctor, in which case an accurate clinical diagnosis depends heavily on obtaining a thorough clinical history from the patient and/or witnesses. Distinguishing between symptoms such as dysphasia (disorder of the production and/or comprehension of speech) and dysarthria (disorder of the articulation of sounds, i.e. slurred speech) for example can be especially difficult when relying on clinical history alone, and may lead to misclassification between lacunar and mild cortical stroke (Lindley *et al*. 1993). Assessment of acutely ill stroke patients is particularly difficult, since patients can be confused, dysphasic and/or drowsy.

In a clinical and brain imaging-based classification, the clinical classification can be modified. For example, if a patient presents with a lacunar syndrome, but has a

small cortical infarct on brain imaging that would explain the patient's symptoms, the classification can be altered from LACI to PACI, thus reducing the proportion of ischaemic stroke subtypes misclassified. The disadvantage of the OCSP is the potential for misclassification when no brain imaging is performed, or brain imaging is performed but reveals no visible acute lesion, in which case the classification is based solely on the clinical symptoms and signs. When CT brain imaging is used, a visible relevant lesion is present in about two thirds of patients, and reliability studies have shown that in the remaining one third of patients who have no visible lesion, the clinical OCSP classification correctly predicts site and size of lesion in about three quarters of patients (Mead *et al*. 2000).

1.3.2 Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification

Other classification methods classify ischaemic stroke subtypes according to the presumed aetiological mechanism. The most commonly used is the TOAST classification, in which an ischaemic stroke is classified as being due to: small vessel disease; atherothrombosis (or large vessel disease); cardioembolism; an undetermined cause (due to incomplete investigation, the existence of more than one potential cause, or no evident cause despite complete investigation); and "other causes" (which includes unusual causes such as arterial dissection and monogenic disorders) (Appendix 2). The inter-observor reliability of this classification method is similar to that of the OCSP, with two studies reporting moderate agreement between assessing neurologists (Adams *et al*. 1993; Gordon *et al*. 1993). The TOAST classification is heavily dependent on clinical investigations such as carotid doppler ultrasound and echocardiogram, and in centres where these investigations are less readily available or are not performed routinely because they are unavailable or

deemed not to change clinical management, the undetermined category of the TOAST classification can include up to about 40% of patients. Even in centres where these types of investigations are carried out the proportion categorised as undetermined can be quite large, because patients often have no detectable aetiological reason for their stroke occurring, or have more than one potential cause. Furthermore, definitions of ischaemic stroke subtypes within the TOAST classification are also risk factor-dependent, with the presence or absence of particular risk factors, such as hypertension, diabetes, cardioembolic source and carotid stenosis influencing classification. This is an important source of potential bias in research studies of the associations between ischaemic stroke subtypes and risk factors.

1.4 Lacunar ischaemic stroke is not a benign disorder

As described, lacunar stroke accounts for about a quarter of all ischaemic strokes in Caucasian populations, and it may be more prevalent in some other ethnic groups. In the past lacunar ischaemic stroke was considered to have a relatively benign prognosis, in comparison to other types of ischaemic stroke. However, that view is changing, as although the short term outcome - in terms of case-fatality - of patients with lacunar ischaemic stroke may be more favourable than that of other subtypes of stroke, in the long term lacunar stroke carries a greater risk of death, morbidity, recurrent stroke and cognitive decline than was previously realised (Norrving 2008), although the differences in outcome between patients with lacunar versus other ischaemic stroke subtypes remain to be clearly established. Given that lacunar ischaemic stroke accounts for such a large proportion of stroke, and carries a substantially worse prognosis than was once thought, a better understanding of the

underlying arterial pathology is clearly needed. At present, acute treatment and secondary prevention of ischaemic stroke is essentially similar across all subtypes of ischaemic stroke. This is largely because the evidence base is randomised controlled clinical trials that do not have the power to investigate differences in treatment effects between ischaemic stroke subtypes. Furthermore, ischaemic stroke subtypes in such trials have often not been well characterised. However, if lacunar ischaemic stroke is caused by a distinct intrinsic small vessel disease, then unravelling the nature of this arteriopathy could lead to more targeted and effective therapeutic options for acute treatment of lacunar ischaemic stroke, prevention of recurrent stroke, and improvement in long-term morbidity and cognitive function.

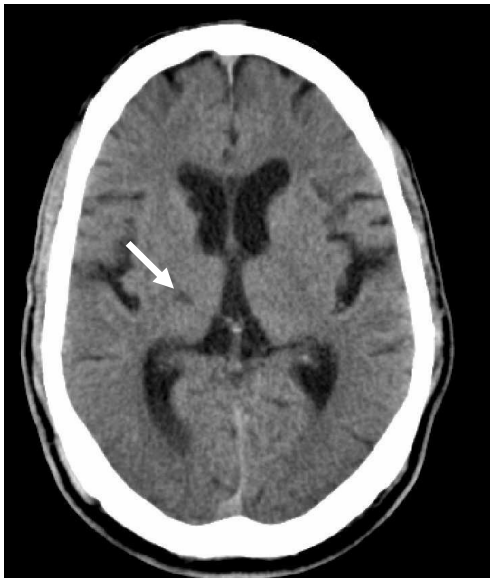
Chapter 2. Unravelling the arterial pathology of lacunar ischaemic stroke

2.1 Lacunar ischaemic stroke

Most lacunar ischaemic stroke manifests clinically as one of five main clinical lacunar syndromes: pure sensory; pure motor; sensorimotor stroke; clumsy-hand dysarthria and ataxic hemiparesis (Norrving 2008). These symptoms result from infarction in the deep subcortical areas of the brain which, when visible on CT brain imaging, appears as a small focal area of hypointensity ≤ 20 mm in diameter (Figure 2.1a).

Figure 2.1 Computed tomography brain imaging, demonstrating (a) a typical lacunar infarct (arrow) and (b) a large cortical infarct (arrow)

(a)



(b)

This small area of infarction is thought to result from the occlusion, or perhaps leakiness (Wardlaw *et al*. 2009), of a single perforating artery supplying the deep subcortical areas of the brain. These arteries include the lenticulostriate arteries, which arise from the mainstem of the middle cerebral artery (Figure 2.2). The arterial processes leading to lacunar infarction are thought by many to differ from the atherothrombotic processes that occlude larger intra- and extra-cranial arteries causing most other types of ischaemic stroke (Figures 2.1 and 2.2). However, the location and small size of the perforating arteries make investigation of the vascular pathological processes leading to lacunar infarction extremely challenging.

Figure 2.2 Pictorial depictions of (a) presumed occlusion of lenticulostriate arteries resulting in lacunar infarction and (b) occlusion of the middle cerebral artery causing a large cortical infarct

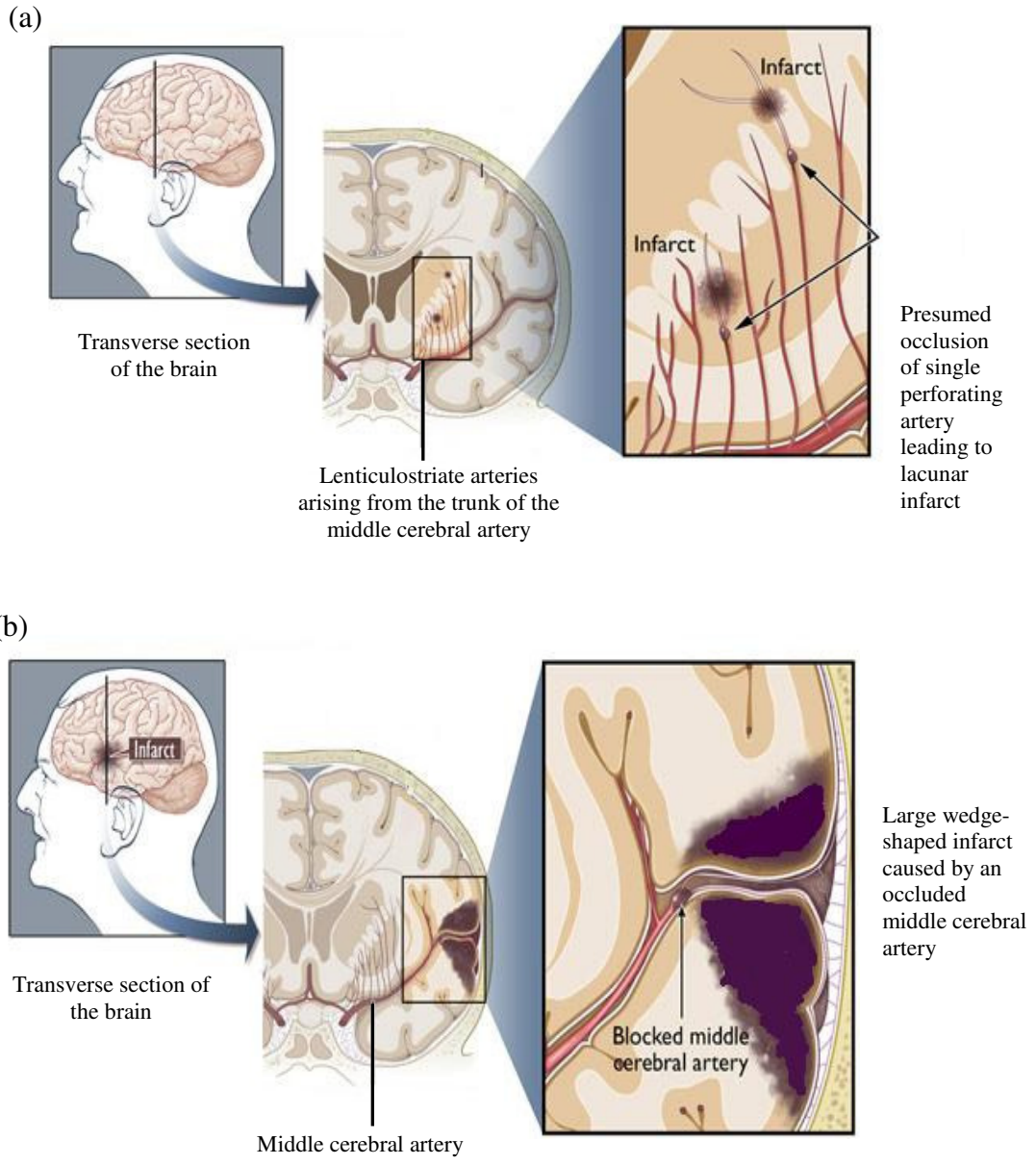
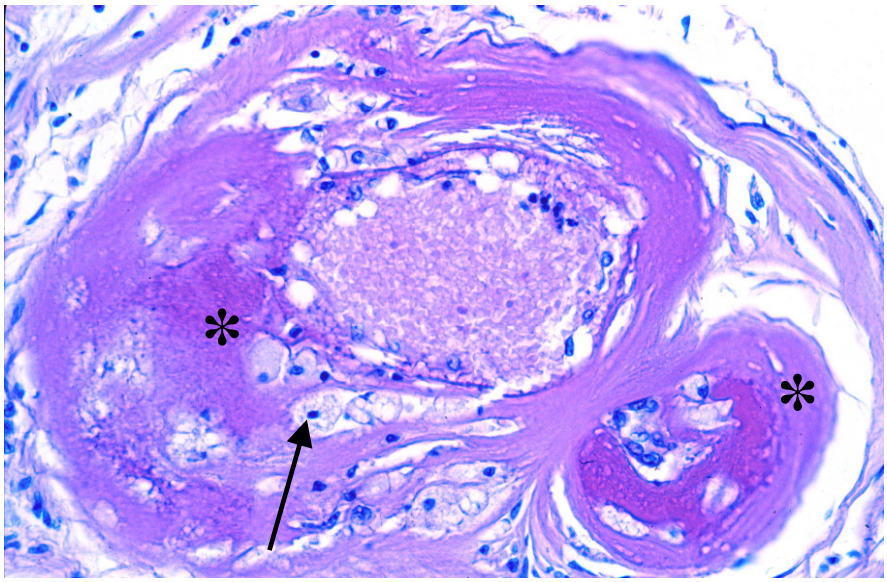


Figure adapted from http://uwmedicine.washington.edu/uwmed

2.2 Pathological evidence for a distinct lacunar arteriopathy

Much of our current understanding of the arterial pathology of lacunar ischaemic stroke is based on Miller Fisher's meticulous clinicopathological studies from the 1960s and 1970s. During this time he serially dissected the vascular supply of 68 lacunar infarcts in 18 postmortem brains of patients who had had either a clinical lacunar stroke or a posterior circulation stroke thought to be due to infarction in the territory supplied by the perforating pontine arteries that arise from the basilar artery (Fisher 1968; Fisher 1971; Fisher 1977; Fisher 1978; Fisher 1979; Fisher & Tapia 1987). He reported that most symptomatic lacunar infarcts were associated with the narrowing or sometimes occlusion of perforating arteries 200-800 μm in diameter by atheromatous plaques - sometimes largely composed of lipid-containing macrophages - with or without complicating thrombus. This small vessel atherosclerosis was found particularly in the basilar artery and its pontine perforating branches (Fisher 1977; Fisher 1987; Fisher 1971). He also reported that most asymptomatic lacunar infarcts - caused by disruption of the blood flow in small perforating arteries of about 40-200 μm in diameter - were associated with lipohyalinosis. This destructive small vessel lesion is characterised in the acute phase by fibrinoid necrosis and in the healed phase by arterial wall disorganisation, collagenous sclerosis, and lipid-containing macrophages (Figure 2.3).

Figure 2.3 Pathological cross-section of a lenticulostriate artery with lipohyalinosis, showing an asymmetric, disorganised arterial wall with fibrinoid material (*) and mural foam cells (arrow)



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Miller Fisher's pathological observations without doubt made an important contribution to our understanding of the arteriopathy of lacunar ischaemic stroke. However, a number of limitations make it difficult to draw firm conclusions from these pathological studies. The number of patients included was small (18 patients in total), most of the lacunar infarcts were asymptomatic, and infarcts related to stroke symptoms were studied months or even years after the acute event. Furthermore, in the study in which the majority of infarcts were described (50 lacunes in four patients), all patients had hypertension, three of whom had severe hypertension. Indeed, it is likely that the presence of hypertension was the reason for their inclusion in the study. Miller Fisher's findings are therefore based largely on the study of a very select group of patients who are probably not representative of those with

lacunar ischaemic stroke, particularly in the present day when severe hypertension is far less common.

2.3 Theories and controversies surrounding lacunar stroke arteriopathy

Since Miller Fisher's studies, further progress in understanding the arteriopathy of lacunar ischaemic stroke has been limited, for three main reasons. First, direct evidence from pathological studies is limited. Lacunar ischaemic stroke has a low early case fatality rate (Bamford *et al*. 1987), and thus autopsies soon after stroke are rarely carried out. This is compounded by the overall decline in autopsy rates during the last 30 to 40 years (Burton *et al*. 2007). In addition, tracing the vascular supply of areas of subcortical infarction is technically demanding, time consuming and expensive. Second, informative brain imaging studies are scarce due to the difficulties of directly visualising *in vivo* the small perforating arteries. Third, there is a lack of suitable, informative animal models for lacunar ischaemic stroke, although the spontaneous hypertensive stroke-prone rat is perhaps a good model for some aspects of the disease (Bailey *et al*. 2009).

In the absence of informative modern autopsy data, the relative importance of lipohyalinosis and atherosclerosis to the cause of lacunar infarction therefore remains unclear, and the initiating arterial changes leading to infarction and these pathological features observed at autopsy are still unknown. Furthermore, a particular limitation of autopsy studies is that it is difficult to distinguish between pathological changes that actually caused the brain injury from those that represent a response to brain injury.

Given that lipohyalinosis and intracranial atherosclerosis were found by Miller Fisher and others to be associated with thickening of the small vessel wall and

narrowing of the lumen, the assumption was that this narrowing led to vessel occlusion, resulting in lacunar infarction. However, whether lacunar infarction is actually caused by occlusion has recently been questioned, and it has been suggested that specific small vessel arterial changes may initiate the cascade of events leading to lacunar infarction (Wardlaw *et al*. 2003). One hypothesis is that endothelial dysfunction may lead to alteration of the permeability of the blood-brain barrier, extravasation of plasma components into the vessel wall and surrounding brain tissues, and ultimately neuronal damage and infarction (Wardlaw *et al*. 2003). Although there are reports that patients with lacunar ischaemic stroke have elevated levels of markers of endothelial activation and damage (Hassan *et al*. 2003; Hassan *et al*. 2004), and reduced endothelial function (Pretnar-Oblak *et al*. 2006), a major limitation is the lack of a cortical ischaemic stroke control group in these studies to demonstrate that endothelial dysfunction is a specific characteristic of lacunar ischaemic stroke, and not ischaemic stroke in general. One recent study of blood-brain barrier leakiness in patients with lacunar ischaemic stroke did include a control group of patients with cortical ischaemic stroke, and found that increased leakiness in arteries of the brain was present in patients with lacunar stroke (Wardlaw *et al*. 2009). It has also been suggested that lacunar infarction may be one manifestation of a spectrum of consequences of small vessel disease, supported in part by the observed association between lacunar infarction and cerebral white matter lesions (which are associated with vascular dementia) (Inzitari 2003) and microhaemorrhages (Kato *et al*. 2002; Wardlaw *et al*. 2006). However, although blood brain barrier leakage may be consistent with causing diffuse, widespread white

matter lesions, there is some doubt as to whether such processes could cause the focal, well demarcated lesions that result in lacunar ischaemic stroke (Kalimo 2003). The aetiology of lacunar ischaemic stroke is still controversial, and there is an ongoing debate as to whether an intrinsic small vessel disease is indeed responsible for most lacunar stroke (Futrell 2004; Millikan & Futrell 1990; Norrving 2004). The extent to which cardiac or carotid emboli cause lacunar ischaemic stroke is one particular area of controversy (Futrell 2004; Millikan & Futrell 1990; Norrving 2004). Many believe that embolism is the cause of only a minority of strokes, with the majority due to intrinsic small vessel disease (Norrving 2004), whereas others propose that the importance of embolism as a causal mechanism is underestimated (Futrell 2004). The advent of new neuroimaging techniques, particularly diffusion weighted magnetic resonance imaging (which is very sensitive to small lesions, especially in the very acute period), has perhaps re-ignited this debate. Multiple acute infarction patterns on diffusion weighted magnetic resonance imaging have been associated with cardiac or carotid sources of emboli, and some have suggested that when embolic patterns of infarction on advanced brain imaging are taken into account, 30-40% of lacunar strokes may be considered to be attributed to atherothromboembolism (Caso *et al*. 2005; Wessels *et al*. 2005). However, these results contrast with those from another recent study in which the frequency of such embolic patterns was much lower, and the prevalence of definite embolic mechanisms (such as atrial fibrillation) similar to that reported in patients with single lacunar infarcts (Chowdhury *et al*. 2004). Such ischaemic lesion patterns may be in keeping with an embolic mechanism of stroke, but as argued by some, may also reflect an underlying diffuse small vessel disease (Chowdhury *et al* 2004).

The difficulty of studying the aetiology of lacunar stroke is compounded by the co-existence of multiple risk factors for stroke, and sometimes more than one possible mechanism of stroke. In elderly patients the existence of coincidental abnormalities is to be expected and the contribution of various risk factors, including some cardiac abnormalities, to ischaemic stroke, and to lacunar stroke in particular, remains uncertain.

2.4 An epidemiological approach to studying the aetiology of lacunar stroke

Given the difficulties and limitations of the more direct approaches to investigating the arterial pathology of lacunar stroke, one indirect approach is to use observational studies to compare the epidemiological features of patients with lacunar versus non-lacunar ischaemic stroke, since differences might provide evidence for, and information about, a distinct underlying lacunar arteriopathy. There may be differences in the risk factor profiles, and in the risks of vascular outcomes including recurrent stroke and myocardial infarction. To date, many such observational studies have been limited by methodological shortcomings, the potential effects of which have often been overlooked. We aimed to address many of these methodological shortcomings in the Edinburgh Stroke Study, a cohort study of patients recruited from our hospital and followed for up to four years for death and recurrent vascular events. Through systematic review of the literature and analysis of data from the Edinburgh Stroke Study and from other similar stroke registers, I addressed the following aim and objectives in this thesis:

2.4.1 Aim and objectives of thesis

My aim was to compare the epidemiological features of patients with lacunar ischaemic stroke versus those with non-lacunar ischaemic stroke, with the hypothesis

that differences in epidemiology may reflect and inform about the underlying arteriopathy of lacunar ischaemic stroke.

My specific objectives were:

1. to systematically review and synthesise (using meta-analysis where appropriate) the existing published data on the risk factor profiles of patients with lacunar compared with non-lacunar ischaemic stroke;
2. to systematically review and synthesise (using meta-analysis where appropriate) the existing published data on outcome, in terms of death and recurrent vascular events, among patients with lacunar compared with non-lacunar ischaemic stroke;
3. to carry out an individual patient data analysis of ischaemic stroke subtype-risk factor associations by pooling data from the Edinburgh Stroke Study with individual patient data from stroke registers from around the world that used a similar methodology;
4. to determine and compare the outcome, in terms of death, recurrent stroke and myocardial infarction, of patients with lacunar versus non-lacunar ischaemic stroke using data from the Edinburgh Stroke Study.

Chapter 3. Risk factor profiles of lacunar versus non-lacunar ischaemic stroke: a systematic review and meta-analysis

3.1 Aim

In this chapter I will present the results of my systematic review and meta-analysis of studies comparing risk factor profiles of lacunar versus non-lacunar ischaemic stroke.

3.2 Introduction

Various classical risk factors, including vascular risk factors such as hypertension, diabetes mellitus and atrial fibrillation (Burchfiel *et al*. 1994; MacMahon *et al*. 1990; Prospective Studies Collaboration 2002; Rodgers *et al*. 1998; Wolf *et al*. 1991), and lifestyle risk factors such as cigarette smoking and alcohol excess (Hankey 1999; Reynolds *et al*. 2003), are known independently to increase the risk of ischaemic stroke. What is less clear is how the risk factor profiles of different subtypes of ischaemic stroke differ. Prospective studies of healthy individuals in whom risk factors were measured at baseline and stroke outcome data were collected have rarely distinguished between pathological types or subtypes of stroke (Prospective Studies Collaboration 2002; Rodgers *et al*. 1998). Comparison of the risk factor profiles of lacunar versus non-lacunar ischaemic stroke may however reveal important differences that may suggest that there is a distinct lacunar arteriopathy. Hypertension and diabetes, for example, are major risk factors for all types of stroke, but are commonly believed to be particularly important in the causation of lacunar ischaemic stroke (Mohr & Stein 1998). As described in the previous chapters, much of the current knowledge of the arterial pathology of lacunar ischaemic stroke is

based largely on Miller Fisher's meticulous clinicopathological studies (Fisher 1968; Fisher 1977; Fisher 1978; Fisher 1979; Fisher & Tapia 1987). These studies also led Miller Fisher to hypothesise that hypertension is a major causative factor in the pathogenesis of lacunar ischaemic stroke. In an autopsy study of 1042 patients from a general medical ward, he identified one or more lacunes in 114 patients. Since 111 of these patients were found retrospectively to have a history of hypertension, Miller Fisher concluded that hypertension was a central causative factor for lacunar ischaemic stroke (Fisher 1965). However, in only eight patients did the lacunes identified at autopsy correlate with the patient's clinical presentation, indicating that the vast majority of the infarcts Miller Fisher studied were in fact asymptomatic. Diabetes has perhaps been considered to play a particular role in lacunar ischaemic stroke because it is known to be a risk factor for small artery occlusive disease affecting distal extremities and organs such as the kidney and retina. The clinicopathological correlation between diabetes and lacunar ischaemic stroke is uncertain, with autopsy studies reporting conflicting results (Fisher CM 1965; Tuszynski *et al*. 1989). Yet, as with hypertension, the belief that diabetes is particularly important in lacunar stroke has become entrenched in the literature and clinical teaching (Mohr & Stein 1998; Weisberg 1988).

Since Miller Fisher's clinico-pathological studies, further support for the particular role of hypertension in the pathogenesis of lacunar ischaemic stroke has stemmed from cross-sectional epidemiological studies comparing the risk factors of patients with lacunar and non-lacunar ischaemic stroke. However, the findings from these studies have been inconsistent, and much controversy persists, particularly with respect to the relative importance of hypertension and diabetes in lacunar compared

with non-lacunar stroke. While some researchers have found that these risk factors predispose more to lacunar than non-lacunar ischaemic stroke, others suggest that they are no more common in patients with lacunar than non-lacunar ischaemic stroke. Several methodological problems limit the interpretation of the results of these epidemiological studies. Perhaps most importantly, studies have used a variety of different classification methods to define lacunar and other ischaemic stroke subtypes. Some used a classification primarily based on the clinical features of the stroke syndrome, which was usually refined by the results of brain imaging – i.e. if a patient's computed tomography (CT) and / or magnetic resonance (MR) brain scan showed an infarct that was relevant to the presenting syndrome but whose site and size suggested a different stroke subtype classification from the clinical features alone, the patient was re-classified in line with the imaging findings. Other studies, however, have included potential risk factors such as hypertension in their stroke subtype definitions, which could clearly bias the results of a comparison of the prevalence of such risk factors between subtypes. Some studies have relied on imaging findings alone to classify stroke subtypes, regardless of the patients' symptoms. Some patients in these studies may have been classified on the basis of asymptomatic or remotely symptomatic visible infarcts. Furthermore, patients with a definite ischaemic stroke but no visible infarct would not have been included.

To critically appraise and summarise the existing published data in this area, I performed a systematic review and a series of meta-analyses of studies comparing the prevalence of risk factors in patients with lacunar versus non-lacunar ischaemic stroke. In my meta-analyses I focused in particular on investigating the effect of the

method of classifying subtypes of ischaemic stroke subtypes on risk factor-stroke subtype associations.

3.3 Methods

3.3.1 Study identification

I sought studies comparing the prevalence of risk factors among patients with stroke attributable to lacunar versus non-lacunar cerebral infarction and published in English up to and including November 2006. I identified studies by a comprehensive text word and MeSH-based electronic search of Medline and Embase, which was designed to identify articles relating to ischaemic stroke subtypes, especially lacunar strokes (Appendices 3 and 4); perusal of the reference lists of relevant articles identified; searching within books on cortical and subcortical strokes; and through discussions with colleagues.

I selected potentially relevant studies from those identified in the search strategy, and discussed inclusion or exclusion of each study with a second reviewer (CLMS). Following these discussions, we decided that only studies published from 1985 onwards should be included because the few earlier studies had very limited access to brain imaging, which was often restricted to younger patients. I excluded studies that included highly selected groups of patients such as randomised controlled trials, studies in which the method used to classify ischaemic stroke subtypes was unclear, and studies where there were data inconsistencies or the data were in a non-extractable format.

3.3.2 Data extraction

From each included study, I extracted data on:

- the population studied (community-based or hospital-based; inpatients or outpatients; consecutive recruitment or not)
- the method of classifying ischaemic stroke subtypes
- the proportion of males overall and in lacunar and non-lacunar groups
- the mean (or median) age of patients overall and in lacunar and non-lacunar groups
- the proportion of the study population with CT and/or MR brain imaging;
- the definitions of risk factors
- and the numbers of lacunar and non-lacunar patients with each of the following risk factors: hypertension; diabetes; ischaemic heart disease; atrial fibrillation; carotid stenosis; smoking; previous transient ischaemic attack (TIA); alcohol excess; and raised cholesterol.

The second reviewer also independently extracted data on risk factor frequency from each study, and we resolved any discrepancies by discussion.

I included in the non-lacunar comparison group all patients with non-lacunar ischaemic stroke apart from the small number of patients with "unusual" causes of stroke (e.g. arterial dissections, non-atherosclerotic vasculopathies or haematological disorders) for studies where these were categorised separately. I included patients with posterior circulation ischaemic stroke (where these patients were presented as a separate group), and patients who were categorised as having an "undetermined" cause of stroke (in studies that used an aetiological classification of ischaemic stroke subtypes) in the non-lacunar comparison group.

3.3.3 Statistical analyses

I stratified studies according to whether the classification used to define ischaemic stroke subtypes included the risk factor under study; included other risk factors, but not specifically the risk factor under study; was based on brain imaging alone; was based on clinical features of the stroke syndrome alone, but not including risk factors, or was based on clinical features of the stroke syndrome refined by brain imaging findings (but not dependent on the presence or absence of risk factors). For each risk factor, I determined study-specific and pooled fixed effects odds ratios (ORs) with 95% confidence intervals (CIs) for lacunar versus non-lacunar ischaemic stroke using Cochrane RevMan software (Cochrane Collaboration 2003), and assessed heterogeneity using the I^2 statistic, which describes the proportion of total variation in study estimates that is due to heterogeneity (Higgins & Thompson 2002). Heterogeneity can be described loosely as mild ($I^2 < 30$), moderate ($30 > I^2 < 50$) or substantial ($I^2 > 50$) (Higgins & Thompson 2002). I determined between-group heterogeneity by subtracting the subgroup χ^2 values from the total χ^2 value.

In a pre-defined sensitivity analysis, I repeated the analyses but excluded patients with a cardioembolic stroke (excluding studies where it was not possible to separate cardioembolic strokes from other aetiological types). In doing so, I was able to make a comparison, albeit crude, between patients with ischaemic stroke caused by presumed small vessel disease versus large vessel disease. The distribution of risk factors and of ischaemic stroke subtypes may differ between hospitalised and non-hospitalised patients. Therefore, to test the robustness of the results of my primary analyses, in a second, post-hoc sensitivity analysis I confined my analyses to

community-based studies, or studies that had recruited consecutive patients from hospital admissions and outpatient clinics.

3.4 Results

From a total of 4939 studies identified from the electronic search strategy, 65 presented risk factor data for ischaemic stroke subtypes and were potentially eligible for inclusion. From these, I excluded 24 studies: two studies published prior to 1985 (Mohr *et al*. 1978; Pullicino *et al*. 1980); 7 studies where the method of classifying ischaemic stroke subtypes was very unclear (Al-Shammri *et al*. 2003; Cupini *et al*. 2002; Dulli *et al*. 1998; Jeng *et al*. 1994; Loeb 1986; Spolveri *et al*. 1998; Yokota *et al*. 2004); one study with data inconsistencies (Falcone *et al*. 2000); one study where the data were presented in a non-extractable format (Tanizaki *et al*. 2000); 10 studies that included highly selected groups of patients (Adams *et al*. 1989; Boiten *et al*. 1996b; Cerrato *et al*. 2002a; Cerrato *et al*. 2002b; Halkes *et al*. 2006; Hupperts *et al*. 1994; Inzitari *et al*. 2000; Lee *et al*. 2002; Nagai *et al*. 2001; Slowik *et al*. 2003); and three studies where there was probable overlap with patient populations in other included studies (Di *et al*. 2006; Iso *et al*. 2004; Loeb 1986; Mannami *et al*. 2004) (Figure 3.1). Where there was definite overlap between patient populations in separately published studies, I included the study with the larger patient population. This left 40 studies (Table 3.1), including 43,989 patients, of whom 13,571 had a lacunar ischaemic stroke and 30,418 a non-lacunar ischaemic stroke.

Figure 3.1 Flow diagram of included studies

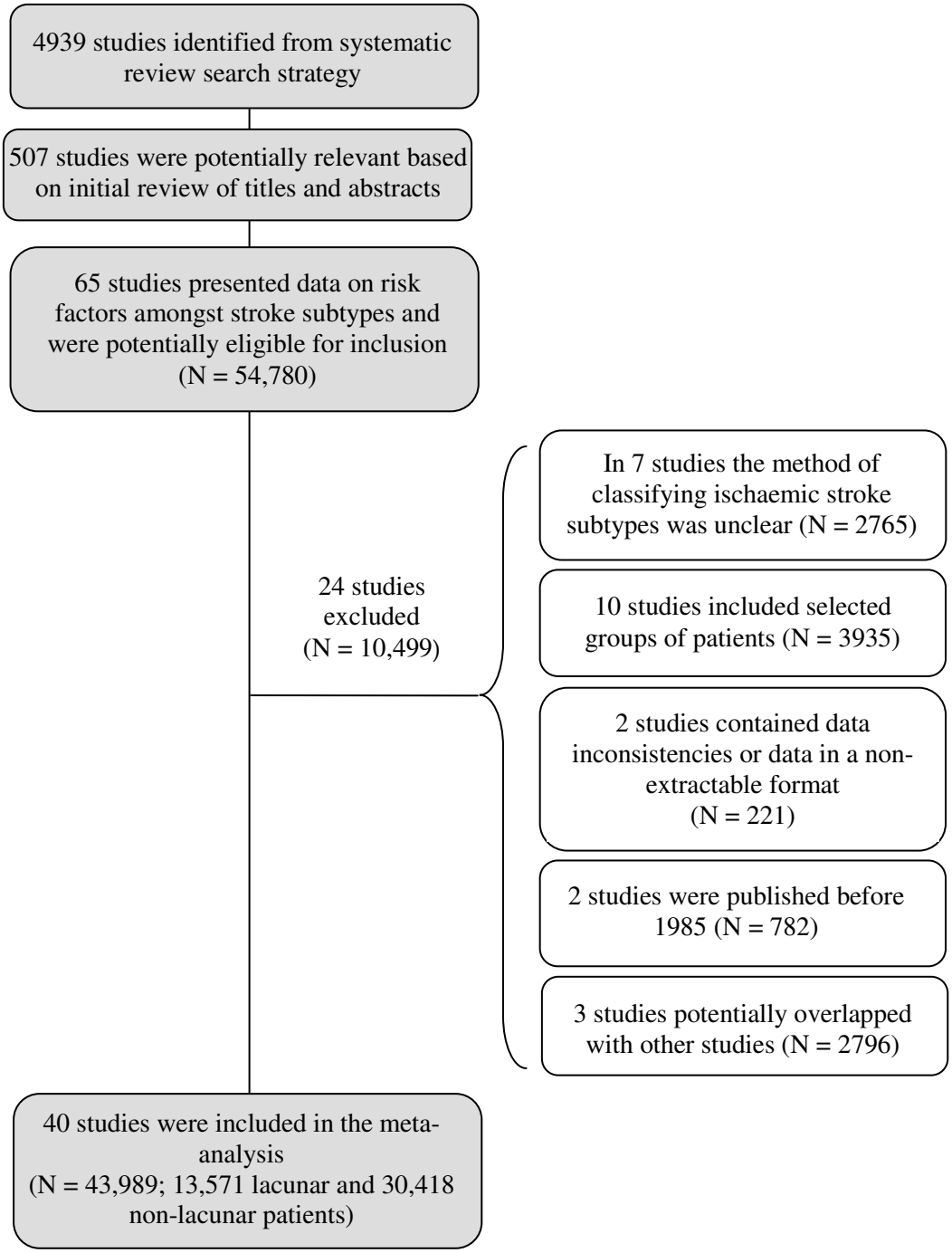


Table 3.1 Characteristics of studies included

Study	Year*	Stroke population recruited	Mean age Lacunar : non-lacunar	% male Lacunar : non-lacunar	% with CT/MR brain scan¶	Ischaemic stroke subtype classification	Non-lacunar comparison group	Risk factors studied	Total ischaemic stroke patients included (lacunar patients)†
Ankara[1]	2002	Consecutive admissions to neurology department with complete evaluation	65 64 : 65	60 65 : 58	100	Risk factor-based (TOAST)	All non-lacunar ischaemic strokes ‡	BP, DM, AF, smoking, HC	264 (66)
Athens[2]	2000	Consecutive admissions	71 67 : 72	58 NR : NR	100#	Risk factor-based (TOAST)	All non-lacunar ischaemic strokes ‡	BP, DM, TIA, AF, smoking, HC	850 (177)
Barcelona[3]	1999	Consecutive admissions	66 67 : 68	57 NR : NR	100	Risk factor-based	All non-lacunar ischaemic strokes ‡	BP, DM, TIA, smoking, HC	2720 (399)
Besançon[4]	2000	Consecutive admissions	69 68 : 69	57 NR : NR	100	Imaging-based	All non-lacunar ischaemic strokes with a single visible infarct on CT/MRI	BP, DM, TIA, AF, smoking, alcohol, HC, IHD	1262 (243)
Boston[5]	2000	Consecutive admissions	69 NR : NR	54 55 : 53	100	Risk factor-based (TOAST)	All non-lacunar ischaemic strokes	BP, DM, AF smoking, alcohol, HC	410 (109)

Table 3.1 (continued)

Study	Year*	Stroke population recruited	Mean age Lacunar : non-lacunar	% male Lacunar : non-lacunar	% with CT/MR brain scan¶	Ischaemic stroke subtype classification	Non-lacunar comparison group	Risk factors studied	Total ischaemic stroke patients included (lacunar patients)†
Buenos Aires[6]	2001	Consecutive admissions	64 62 : 66	64 70 : 58	100	Risk factor-based (TOAST)	All non-lacunar ischaemic strokes ‡	BP, DM, AF, smoking, alcohol, HC, IHD	234 (105)
Cincinnati[7]	1999	Admissions or autopsied cases (among blacks)	NR NR : NR	NR NR : NR	97 #	Risk factor-based (NINDS)	All non-lacunar ischaemic strokes ‡	BP, DM, smoking	167 (39)
Dublin[8]	2003	Admissions via emergency department	70 67 : 72	58 56 : 59	96	Risk factor-free (clinical syndrome not modified by imaging)	All non-lacunar ischaemic strokes	BP, DM, AF, smoking, IHD	117 (48)
Edinburgh[9]	1999	Consecutive admissions and neurovascular clinic outpatients	NR NR : NR	NR NR : NR	NR	Risk factor-free (clinical and imaging-based)	Partial anterior circulation strokes (TACI and POCI excluded)	Ipsilateral CS	608 (215)

Table 3.1 (continued)

Study	Year*	Stroke population recruited	Mean age Lacunar : non-lacunar	% male Lacunar : non-lacunar	% with CT/MR brain scan¶	Ischaemic stroke subtype classification	Non-lacunar comparison group	Risk factors studied	Total ischaemic stroke patients included (lacunar patients)†
Erlangen[10]	2001	Community-based (13% of original cohort excluded due to incomplete investigation)	73 71 : 74	44 NR :NR	100	Risk factor-based (TOAST)	All non-lacunar ischaemic strokes‡	BP, DM, smoking, IHD	522 (120)
Germany[11]	2001	Admissions (multicentre)	68 NR : NR	58 60 : 57	100	Risk factor-based (modified TOAST)	All non-lacunar ischaemic strokes‡	BP, DM, TIA, smoking, alcohol, HC, IHD	4842 (1028)
Grenoble[12]	2006	Admissions (multicentre) within a week of onset	66** 68 : 66	62 63 : 60	100	Imaging-based	All non-lacunar ischaemic strokes	BP, DM, smoking, HC	407 (105)
Hungary[13]	2002	Consecutive admissions to hospital	NR NR : NR	NR NR : NR	NR	Risk factor-based (NINDS)	All non-lacunar ischaemic strokes‡	BP, IHD	435 (136)
Istanbul[14]	2005	Consecutive admissions	64** NR : NR	50 54 : 43	100	Risk factor-free (clinical and imaging-based)	All non-lacunar ischaemic strokes	BP, DM, IHD, TIA, smoking, alcohol, HC	424 (272)

Table 3.1 (continued)

Study	Year*	Stroke population recruited	Mean age Lacunar : non-lacunar	% male Lacunar : non-lacunar	% with CT/MR brain scan¶	Ischaemic stroke subtype classification	Non-lacunar comparison group	Risk factors studied	Total ischaemic stroke patients included (lacunar patients)†
Izmir[15]	1997	Consecutive admissions to stroke care unit	63 NR : NR	56 NR : NR	100	Risk factor-based (TOAST)	All non-lacunar ischaemic strokes	BP, DM, TIA, smoking, HC, ipsilateral CS, IHD	1529 (198)
Japan[16]	2004	Consecutive admissions within 7 days of onset (multicentre)	71 70 : 72	NR NR : NR	100	Risk factor-based (NINDS)	All non-lacunar ischaemic strokes	BP, DM, AF, smoking, HC	14864 (6146)
Jordan[17]	2004	Retrospective review of medical notes for consecutive patients admitted through the ER	61 NR : NR	56 NR : NR	100	Risk factor-based (TOAST)	All non-lacunar ischaemic strokes, excluding CE strokes or strokes of uncertain or mixed aetiology	BP, DM, IHD, TIA, smoking, HC	143 (103)

Table 3.1 (continued)

Study	Year*	Stroke population recruited	Mean age Lacunar : non-lacunar	% male Lacunar : non-lacunar	% with CT/MR brain scan ¶	Ischaemic stroke subtype classification	Non-lacunar comparison group	Risk factors studied	Total ischaemic stroke patients included (lacunar patients) †
L'Aquila[18]	2006	Community-based (only including those patients who had brain imaging – 74% of original cohort)	74 73 : 75	47 51 : 46	100	Risk factor-free (clinical and imaging-based)	Non-lacunar ischaemic strokes with no lacunar lesions on brain imaging	BP, DM, IHD, AF, smoking, HC, ipsilateral CS	2644 (491)
Leon[19]	2003	Admissions to neurology ward with carotid territory infarction and no cardiac source of embolism	67 67 : 67	73 74 : 73	100	Imaging-based	Supratentorial non-lacunar ischaemic strokes excluding CE strokes	BP, DM, IHD, TIA, smoking, Alcohol,	330 (205)

Table 3.1 (continued)

Study	Year*	Stroke population recruited	Mean age Lacunar : non-lacunar	% male Lacunar : non-lacunar	% with CT/MR brain scan¶	Ischaemic stroke subtype classification	Non-lacunar comparison group	Risk factors studied	Total ischaemic stroke patients included (lacunar patients)†
London[20]	2001	Community-based	72 NR : NR	48 NR : NR	NR	Risk factor-free (clinical and imaging-based)	All non-lacunar ischaemic strokes	BP, DM, AF, smoking, alcohol, IHD	862 (282)
Lund (a)[21]	1989	Consecutive admissions with CT brain and catheter angiography, to Neurology department	58 58 : 59	75 67 : 84	100	Risk factor-free (clinical and imaging based)	Non-lacunar ischaemic strokes excluding potentially CE strokes	BP, DM, TIA, smoking, alcohol, HC, ipsilateral CS, contralateral CS, IHD	122 (61)
Lund (b)[22]	1994	Consecutive admissions with brain imaging, carotid ultrasound and ECG	73 NR : NR	55 NR : NR	100	Risk factor-free (clinical syndrome, not modified by imaging)	All non-lacunar ischaemic strokes	AF, ipsilateral CS	166 (49)

Table 3.1 (continued)

Study	Year*	Stroke population recruited	Mean age Lacunar : non-lacunar	% male Lacunar : non-lacunar	% with CT/MR brain scan¶	Ischaemic stroke subtype classification	Non-lacunar comparison group	Risk factors studied	Total ischaemic stroke patients included (lacunar patients)†
Maastricht (a)[23]	1991	Admissions, excluding posterior circulation strokes	70 67 : 71	NR NR : NR	100	Risk factor-free (clinical and imaging-based)	Atherothrombotic strokes (excluding CE strokes for all comparisons except AF)‡	BP, DM, AF, ipsilateral CS, contralateral CS, IHD	247 (103)
Maastricht (b)[24]	1996	NR	NR NR : NR	NR NR : NR	NR	Risk factor-free (clinical and imaging-based)	Non-lacunar ischaemic strokes	BP, DM, IHD	869 (287)
Manchester[25]	1998	Acute stroke admissions	NR NR : NR	NR NR : NR	56§	Risk factor-free (clinical syndrome, not modified by imaging)	All non-lacunar ischaemic strokes (excluding POCI for CS analysis)	AF, ipsilateral CS, contralateral CS	305 (80)
Nanjing[26]	2006	Admissions within 7 days of symptom onset, minus patients lost to follow-up	68 67 : 69	66 67 : 66	100	Risk factor-based (modified TOAST)	All non-lacunar ischaemic strokes	BP, DM, IHD, TIA, AF, smoking, alcohol, HC	610 (123)

Table 3.1 (continued)

Study	Year*	Stroke population recruited	Mean age Lacunar : non-lacunar	% male Lacunar : non-lacunar	% with CT/MR brain scan¶	Ischaemic stroke subtype classification	Non-lacunar comparison group	Risk factors studied	Total ischaemic stroke patients included (lacunar patients)†
Oxford (a)[27]	1990	Community-based	73 72 : 41	49 73 : 53	85§	Risk factor-free (clinical and imaging-based)	Non-lacunar carotid territory ischaemic strokes	BP, DM, TIA, AF, smoking, IHD	304 (102)
Oxford (b)[28]	2003	Community-based	NR NR : NR	52 35 : 56	NR	Risk factor-based (modified TOAST)	All non-lacunar ischaemic strokes	BP, DM, TIA, smoking	101 (20)
Palermo[29]	2006	Consecutive admissions to department of internal medicine and cardio-angiology	62 61 : 62	58 58 : 58	100	Risk factor-based (modified TOAST)	All non-lacunar ischaemic strokes	BP, DM, TIA, smoking, HC	147 (38)
Perugia[30]	2006	Admissions	NR NR : NR	50 55 : 48	100	Risk factor-based (TOAST)	All non-lacunar ischaemic strokes	BP, DM, TIA, smoking, alcohol, HC	1649 (642)

Table 3.1 (continued)

Study	Year*	Stroke population recruited	Mean age Lacunar : non-lacunar	% male Lacunar : non-lacunar	% with CT/MR brain scan¶	Ischaemic stroke subtype classification	Non-lacunar comparison group	Risk factors studied	Total ischaemic stroke patients included (lacunar patients)†
Riyadh[31]	1999	Consecutive admissions with brain imaging	59 NR : NR	68 NR : NR	100	Risk factor-based	All non-lacunar ischaemic strokes	BP, DM, AF, IHD, smoking,	756 (248)
Rochester[32]	1999	Community-based	76 73 : 78	41 43 : 40	92#	Risk factor-based (NINDS)	All non-lacunar ischaemic strokes‡	BP, DM, TIA, smoking, IHD	442 (72)
Rome[33]	1995	Consecutive patients hospitalised within 12 hours of stroke onset	67 67 : 68	58 65 : 55	100	Risk factor-free (clinical and imaging-based)	All non-lacunar carotid territory ischaemic strokes	BP, DM, TIA, AF, smoking	517 (170)
San Diego[34]	1993	Consecutive admissions to and outpatients seen at hospital	61 NR : NR	66 NR : NR	98#	Risk factor-based (TOAST)	All non-lacunar ischaemic strokes‡	BP, DM, TIA, smoking, IHD	448 (133)

Table 3.1 (continued)

Study	Year*	Stroke population recruited	Mean age Lacunar : non-lacunar	% male Lacunar : non-lacunar	% with CT/MR brain scan¶	Ischaemic stroke subtype classification	Non-lacunar comparison group	Risk factors studied	Total ischaemic stroke patients included (lacunar patients)†
Seoul (a)[35]	1999	Admissions who had a CT or MRI and catheter angiography	61 61 : 61	76 63 : 83	100	Risk factor-based (modified TOAST)	Large vessel infarcts, excluding CE strokes‡	BP, DM, smoking, alcohol, IHD	153 (49)
Seoul (b)[36]	2001	Admissions within 7 days of stroke onset	62 61 :62	63 64 : 60	100#	Risk factor-based (TOAST)	All non-lacunar ischaemic strokes‡	BP, DM, TIA, smoking, HC	969 (215)
Taiwan[37]	1997	Consecutive admissions	66 66 : 66	57 54 : 58	"Most"	Risk factor-based (TOAST)	All non-lacunar ischaemic strokes‡	BP, DM, AF smoking, alcohol, HC, ipsilateral CS, IHD	637 (195)
Texas[38]	1991	Inpatients and outpatients seen in neurology department	61 61 : 61	75 71 : 80	100	Risk factor-free (clinical and imaging-based)	Non-lacunar carotid territory infarcts, excluding CE and unclassified infarcts	BP, DM, TIA, smoking, ipsilateral CS, contralateral CS	109 (55)
USA (a)[39]	1987	Admissions (multicentre)	68 66 : 69	47 46 : 48	97 #	Risk factor-based (NINDS)	All non-lacunar ischaemic strokes	BP, DM, TIA, AF, IHD	1273 (337)

Table 3.1 (continued)

Study	Year*	Stroke population recruited	Mean age Lacunar : non-lacunar	% male Lacunar : non-lacunar	% with CT/MR brain scan¶	Ischaemic stroke subtype classification	Non-lacunar comparison group	Risk factors studied	Total ischaemic stroke patients included (lacunar patients)†
USA (b)[40]	2006	Community-based (multi-population)	53 56 : NR	57 51 : NR	100	Imaging-based	All non-lacunar ischaemic strokes	BP, DM, smoking, alcohol, IHD	531 (105)

* of publication
† Total of 40 studies with 43,989 ischaemic stroke patients included in the lacunar versus non-lacunar comparisons, and 13571 patients with lacunar ischaemic stroke
‡ Ischaemic strokes with unusual causes excluded - generally < 5% of ischaemic stroke patients studied
§ Siriraj score or Guy's Hospital Stroke Diagnostic Scale was used to distinguish between ischaemic and haemorrhagic stroke in the absence of brain imaging
¶ % of the total number of ischaemic stroke patients included (shown in final column) except where otherwise stated
# % of total cohort studied (all ischaemic strokes ± haemorrhagic strokes)
**median
TOAST = Trial of Org 10172 in Acute Stroke Treatment; NINDS = National Institute of Neurological Disorders and Stroke; OCSP = Oxford Community Stroke Project; TACI = total anterior circulation infarction; POCI = posterior circulation infarction; BP = blood pressure; DM = diabetes mellitus; AF = atrial fibrillation; HC = hypercholesterolaemia; IHD = ischaemic heart disease; CS = carotid stenosis; NR = not reported; MRI = magnetic resonance imaging; CE = cardioembolic; ECG = electrocardiogram.

[1]Murat & Erturk 2002; [2]Vemmos *et al*. 2000; [3]Marti-Vilalta & Arbroix 1999; [4]Moulin *et al*. 2000; [5]Saposnick *et al*. 2000; [6]Saposnick *et al*. 2001; [7]Woo *et al*. 1999; [8]Pittock *et al*. 2002; [9]Mead *et al*. 1999; [10]Kolominsky-Rabas *et al*. 2001; [11]Grau *et al*. 2001; [12]Amarenco *et al.* 2006.; [13]Aszalos *et al*. 2002; [14]Somay *et al*. 2006; [15]Kumral *et al*. 1998; [16]Kimura *et al*. 2004; [17]Bahou *et al*. 2004 ; [18]Sacco *et al*. 2006; [19]Tejada *et al*. 2003; [20]Hajat *et al*. 2001; [21]Norrving & Cronqvist 1989; [22]Lindgren *et al*. 1994; [23]Boiten & Lodder, 1991; [24]Boiten *et al*. 1996; [25]Mead *et al*. 1998; [26]Liu *et al*. 2006; [27]Lodder *et al*. 1990; [28]Schulz *et al*. 2003; [29]Pinto *et al*. 2006; [30]Silvestrelli *et al*. 2006; [31]Awada & Rajeh, 1999; [32]Petty *et al*. 1999; [33]Toni *et al*. 1995; [34]Rothrock *et al*. 1993; [35]Kim & Choi-Kwon 1999; [36]Lee *et al*. 2001; [37]Yip *et al*. 1997; [38]Tegeler *et al.* 1997; [39]Foulkes *et al*. 1998; [40]Ohira *et al*. 2006;

Descriptions of the main types of classification methods used are given in Table 3.2. Twenty-three studies (34,165 patients) used classification methods that included risk factors in the definitions of ischaemic stroke subtypes (Aszalos *et al*. 2002; Awada & Al 1999 ; Bahou *et al*. 2004; Foulkes *et al*. 1988; Grau *et al*. 2001; Kim & Choi-Kwon 1999; Kimura *et al*. 2004; Kolominsky-Rabas *et al*. 1998; Kumral *et al*. 1998; Lee *et al*. 2001; Liu *et al*. 2006; Marti-Vilalta & Arboix 1999; Murat & Erturk 2002; Petty *et al*. 1999; Pinto *et al*. 2006; Rothrock *et al*. 1993; Saposnik *et al*. 2000; Saposnik *et al*. 2001; Schulz & Rothwell 2003; Silvestrelli *et al*. 2002; Vemmos *et al*. 2000; Woo *et al*. 1999; Yip *et al*. 1997). Eleven of these used the original TOAST classification (Bahou *et al*. 2004; Kolominsky-Rabas *et al*. 1998; Kumral *et al*. 1998; Lee *et al*. 2001; Murat & Erturk 2002; Rothrock *et al*. 1993; Saposnik *et al*. 2000; Saposnik *et al*. 2001; Silvestrelli *et al*. 2002; Vemmos *et al*. 2000; Yip *et al*. 1997), in which the presence of hypertension and diabetes favours a diagnosis of lacunar infarction, and carotid stenosis of > 50% and potential sources of cardiac embolism precludes a diagnosis of lacunar infarction. (Table 3.2).

In 5 studies, most of which were published more recently, the authors stated that they used a "modified" TOAST classification (Grau *et al*. 2001; Kim & Choi-Kwon 1999; Liu *et a*l. 2006; Pinto *et al*. 2006; Schulz & Rothwell 2003). This appears to be similar to the original TOAST classification, but does not consider the presence of hypertension and diabetes to favour a diagnosis of lacunar infarction, although a "modified" TOAST classification has not been formally described in the literature. The remaining 8 studies that used a risk factor-based classification method used the National Institute of Neurological Disorders and Stroke (NINDS) classification method (Table 3.2), or similar.

Table 3.2 Descriptions of ischaemic stroke subtype classification methods

Method		Description
Based on risk factors as well as clinical and brain imaging features	TOAST	Ischaemic stroke classified into one of 5 categories: **Large artery atherosclerosis**: Clinical findings include cortical, cerebellar, or brain stem dysfunction and on brain imaging cortical, cerebellar, brain stem or subcortical lesions > 1.5 cm are considered to be of potential large artery atherosclerotic origin. Diagnosis requires supportive evidence by duplex imaging or arteriography of > 50% stenosis of an appropriate intracranial or extracranial artery. Potential sources of cardiogenic embolism, such as AF should be excluded, and history of TIAs in the same vascular territory supports the clinical diagnosis. **Cardioembolism**:Clinical and brain imaging findings are similar to those described for large artery atherosclerosis. At least 1 cardiac source of embolism, such as AF, must be identified. Previous TIAs in > 1 vascular territory supports the diagnosis. Potential large artery atherosclerotic sources of thrombosis or embolism should be absent. **Lacunar**: Clinical findings of one of the lacunar syndromes should be present. Brain imaging should be normal or show a relevant brain stem or subcortical hemispheric lesion of diameter < 1.5 cm. A history of diabetes mellitus or hypertension supports the diagnosis. Potential cardiac sources of embolism, such as AF, should be absent, and the large extracranial arteries should not demonstrate > 50% stenosis. **Undetermined aetiology**: Includes patients with ≥ 2 potential causes of stroke (e.g., AF and > 50% stenosis of extracranial arteries) and patients with an unidentified cause of stroke (following either complete or incomplete investigation **Other determined aetiology**: Includes patients with rare causes of stroke (e.g., non-atherosclerotic vasculopathies and haematologic disorders).
	NINDS	**Large artery atherosclerosis**: Clinical and brain imaging findings as described in TOAST. A history of TIAs is considered more common than among those with other types of stroke. Clinical diagnosis rests on finding evidence of arterial stenosis or occlusion at ≥ 1 sites. **Cardioembolism**: Clinical and brain imaging findings as described in TOAST. The basis for the clinical diagnosis is the demonstration of a cardiac-transcardiac source of embolism (such as AF) and no evidence of other causes of stroke. **Lacunar**: Clinical findings of a lacunar syndrome with normal brain imaging or relevant lesion. No mention of risk factors that specifically support a lacunar diagnosis. **Undetermined aetiology**: Cerebral infarction in the absence of stenosis or occlusion of extracranial or intracranial arteries, cardiac sources of embolism, or other demonstrable mechanism. **Other determined aetiology**: As in TOAST classification.

Table 3.2 (continued)

Method		Description
Based on brain imaging only		Site and size of visible infarction on CT or MRI scan used to classify stroke subtypes irrespective of patient's symptoms. Patients with a definite ischaemic stroke but no visible lesion excluded.
Based on clinical features only	eg, OCSP (not modified by imaging)	Clinical stroke syndrome (eg TACI, PACI, LACI and POCI) used to assign stroke subtype. Syndromes are not revised in light of brain imaging findings.
Based on clinical features and brain imaging	eg, OCSP (modified by imaging)	Clinical stroke syndrome (eg TACI, PACI, LACI and POCI) assigned to each patients, which is then revised in light of site and size of any relevant infarct seen on CT or MRI scan.

TOAST = Trial of Org 10172 in Acute Stroke Treatment; NINDS = National institute of Neurological Disorders and Stroke: Classification of Cerebrovascular Diseases III; AF = atrial fibrillation; TIA = transient ischaemic attack; OCSP = Oxfordshire Community Stroke Project classification; TACI = total anterior circulation stroke; PACI = partial anterior circulation stroke; LACI = lacunar infarction; POCI = posterior circulation infarction.

Four studies (2530 patients) defined ischaemic stroke subtypes on the basis of size and location of infarction on imaging alone (Amarenco *et al*. 2006; Moulin *et al*. 2000; Ohira *et al*. 2006; Tejada *et al*. 2003). In 10 studies (6706 patients), ischaemic subtypes were defined according to the clinical features of the stroke syndrome (but not including risk factors), refined where appropriate by the site and size of any relevant lesion seen on brain imaging (Boiten *et al*. 1996a; Boiten & Lodder 1991; Hajat *et al*. 2001; Lodder *et al*. 1990; Mead *et al*. 1999b; Norrving & Cronqvist 1989; Sacco *et al*. 2006; Somay G *et al*. 2006; Tegeler *et al*. 1991; Toni *et al*. 1995) (Table 3.1). Three studies (588 patients) defined ischaemic subtypes on the basis of clinical features of stroke syndrome but not modified by brain imaging findings (Lindgren *et al*. 1994b; Mead *et al*. 1998; Pittock *et al*. 2003), and in my analyses I grouped these with clinical and imaging-based studies, since the study populations were very small, and excluding them from this category did not affect the summary odds ratio for any risk factor.

7 studies (5406 patients) were community-based, whereas 33 (38,583 patients) were hospital-based, mostly recruiting hospital admissions (Table 3.1). The mean age of the patients was higher in the community- than in the hospital-based studies (weighted mean age 72 versus 68 years), and the proportion of males was lower in the community-based studies (48% versus 58%).

Just over half of all studies included presented the mean ages of lacunar and non-lacunar patients, which were similar (weighted mean 69 versus 70 years). The proportion of males among lacunar patients was slightly higher than among non-lacunar patients (58% versus 54%). Thirty four studies provided data on the number of patients who had brain imaging performed, with 27 studies reporting that 100% of

patients had brain imaging. The non-lacunar comparison group varied across studies, due to the differing methods used to classify ischaemic stroke subtypes and the additional exclusion criteria employed in some studies. Presumed cardioembolic strokes were excluded from the study population in six studies, posterior circulation strokes were excluded in two studies, and total anterior circulation and posterior circulation strokes were excluded in one study (Table 3.1). The definitions of risk factors used by each study are given in Table 3.3.

Table 3.3 Definitions of risk factors in included studies*

	Hypertension		Diabetes†						Severe carotid stenosis	
Study	**Pre/post stroke**	**Cut-off (mm Hg)**	**Pre/post stroke**	**Cut off Fasting or random glucose (mmol/l)#**	**Ischaemic heart disease**	**Smoking**	**Alcohol‡**	**Raised cholesterol (mmol/l)¶**	**Cut-off**	**Method of measurement**
Ankara[1]	Pre or post	160/90	Pre or post	Fasting > 7.8 or random > 11.1	*ND*	Current smoking or within 5 years	*ND*	> 5.7	*ND*	*ND*
Athens[2]	Pre	160/90	Pre	Fasting > 6.0	*ND*	Current daily smoking or within previous year	*ND*	> 6.5	*ND*	*ND*
Barcelona[3]	Pre or post	160/90	Pre or post	Fasting > 6.1	*ND*	Current smoking or within previous 5 years	*ND*	> 6.5 or triglycerides > 1.71	*ND*	*ND*
Besançon[4]	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*ND*	*ND*
Boston[5]	Pre or post	140/90	*NR*	*NR*	*ND*	> 10 cigarettes/day	> 2 units/day	*NR*	*ND*	*ND*
Buenos Aires[6]	Pre or post	140/90	Pre or post	Random > 11	*ND*	> 10 cigarettes/day	> 2 units/day	> 5.7	*ND*	*ND*

Table 3.3 (continued)

	Hypertension		Diabetes†						Severe carotid stenosis	
Study	**Pre/post stroke**	**Cut-off (mm Hg)**	**Pre/post stroke**	**Cut off Fasting or random glucose (mmol/l)#**	**Ischaemic heart disease**	**Smoking**	**Alcohol‡**	**Raised cholesterol (mmol/l)¶**	**Cut-off**	**Method of measurement**
Cincinnati[7]	Pre	*NR*	Pre	*NR*	*ND*	Current smoking	*ND*	*ND*	*ND*	*ND*
Dublin[8]	*NR*	*NR*	*NR*	*NR*	History of MI or angina	Current or ex-smoking	*ND*	*ND*	*ND*	*ND*
Edinburgh[9]	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	> 70%	Ultrasound
Erlangen[10]	Pre or post	160/95	Pre or post	Fasting > 6.7	History of MI, coronary artery disease, congestive heart failure, arrhythmia or valvular heart disease	Current smoking	*ND*	*ND*	*ND*	*ND*
Germany[11]	Pre	160/90	Pre or post	*NR*	*ND*	Current smoking	Daily alcohol consumed	> 5.7 before stroke or on lipid-lowering medication	*ND*	*ND*

Table 3.3 (continued)

	Hypertension		Diabetes†						Severe carotid stenosis	
Study	**Pre/post stroke**	**Cut-off (mm Hg)**	**Pre/post stroke**	**Cut off Fasting or random glucose (mmol/l)#**	**Ischaemic heart disease**	**Smoking**	**Alcohol‡**	**Raised cholesterol (mmol/l)¶**	**Cut-off**	**Method of measurement**
Grenoble[12]	Pre	-	Pre	*NR*	*ND*	Current smoking	*ND*	> 4.1 or on lipid-lowering medication	*ND*	*ND*
Hungary[13]	Pre or post	90/160	*ND*	*ND*	ECG and/or autopsy evidence of IHD	*ND*	*ND*	*ND*	*ND*	*ND*
Istanbul[14]	Pre or post	140/90	Pre or post	Fasting ≥ 7.7	History of angina or MI	Current smoking within the last 12 months	*NR*	Fasting cholesterol > 6.2 or on lipid-lowering medication	*ND*	*ND*
Izmir[15]	Pre	160/90	Pre	Fasting > 6.0	*NR*	Regular smoking	*ND*	> 6.5	> 50 %	Ultrasound, MRA or catheter angiography
Japan[16]	Pre	160/95	Pre or post	*NR*	*ND*	Current smoking	*ND*	≥ 5.7 or on lipid-lowering medication	*ND*	*ND*

Table 3.3 (continued)

	Hypertension		Diabetes†						Severe carotid stenosis	
Study	**Pre/post stroke**	**Cut-off (mm Hg)**	**Pre/post stroke**	**Cut off Fasting or random glucose (mmol/l)#**	**Ischaemic heart disease**	**Smoking**	**Alcohol‡**	**Raised cholesterol (mmol/l)¶**	**Cut-off**	**Method of measurement**
Jordan[17]	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*ND*	*NR*	*ND*	*ND*
L'Aquila[18]	Pre or post	150/90	Pre	Fasting > 7.8	*NR*	Daily smoking within at least last 2 months	≥ 2 units/day for women, ≥ 3 units/day for men	> 5.7	> 50%	Ultrasound
Leon[19]	Pre or post	150/90	Pre or post	Fasting > 7.7	History of MI or angina, or ischaemic type signs on ECG	Current smokers of at least 10 cigarettes/day in the previous 6 months and ex-smokers with a similar consumption for 6 months on a regular basis	>10 unit/days per day	*NR*	*NR*	*NR*
London[20]	Pre	160/95	Pre	Fasting > 7.8	History of MI or angina	Ever smoked	*ND*	*ND*	*ND*	*ND*

Table 3.3 (continued)

	Hypertension		Diabetes†						Severe carotid stenosis	
Study	**Pre/post stroke**	**Cut-off (mm Hg)**	**Pre/post stroke**	**Cut off Fasting or random glucose (mmol/l)#**	**Ischaemic heart disease**	**Smoking**	**Alcohol‡**	**Raised cholesterol (mmol/l)¶**	**Cut-off**	**Method of measurement**
Lund (a)[21]	Pre or post	160/90	*NR*	*NR*	History of MI or isolated angina pectoris	*NR*	Alcohol abuse	*NR*	≥ 50%	Catheter angiography
Lund (b)[22]	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	≥ 50%	Ultrasound
Maastricht (a)[23]	Pre or post	160/90	Pre or post	*NR*	*NR*	*ND*	*ND*	*ND*	≥ 50%	Ultrasound
Maastricht (b)[24]	*NR*	*NR*	*NR*	*NR*	*NR*	*ND*	*ND*	*ND*	*ND*	*ND*
Manchester[25]	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	> 70%	Ultrasound
Nanjing[26]	Pre or post	160/90	Pre or post	Fasting > 7.0	History of MI	*NR*	*NR*	> 5.7 or on lipid-lowering medication	*ND*	*ND*

Table 3.3 (continued)

	Hypertension		Diabetes†						Severe carotid stenosis	
Study	**Pre/post stroke**	**Cut-off (mm Hg)**	**Pre/post stroke**	**Cut off Fasting or random glucose (mmol/l)#**	**Ischaemic heart disease**	**Smoking**	**Alcohol‡**	**Raised cholesterol (mmol/l)¶**	**Cut-off**	**Method of measurement**
Oxford (a)[27]	Pre	160/90	*NR*	*NR*	History of non-rheumatic AF, definite MI, angina or typical ECG changes of MI	Ever smoked	*ND*	*ND*	*ND*	*ND*
Oxford (b)[28]	Pre	160/95	Pre	*NR*	*ND*	Current smoking	*ND*	*ND*	*ND*	*ND*
Palermo[29]	Pre	*NR*	*NR*	*NR*	*ND*	*NR*	*ND*	*NR*	*ND*	*ND*
Perugia[30]	*NR*	*NR*	*NR*	*NR*	*ND*	Current smoking	*NR*	*NR*	*ND*	*ND*
Riyadh[31]	Pre or post	160/90	Pre or post	Fasting > 7.7	History of MI	*NR*	*ND*	*ND*	*ND*	*ND*

Table 3.3 (continued)

	Hypertension		Diabetes†						Severe carotid stenosis	
Study	**Pre/post stroke**	**Cut-off (mm Hg)**	**Pre/post stroke**	**Cut off Fasting or random glucose (mmol/l)#**	**Ischaemic heart disease**	**Smoking**	**Alcohol‡**	**Raised cholesterol (mmol/l)¶**	**Cut-off**	**Method of measurement**
Rochester[32]	*NR*	*NR*	*NR*	*NR*	History of MI or angina	*NR*	*ND*	*ND*	*ND*	*ND*
Rome[33]	*NR*	*NR*	*NR*	*NR*	*ND*	*NR*	*ND*	*ND*	*ND*	*ND*
San Diego[34]	*NR*	*NR*	*NR*	*NR*	*NR*	≥ 5 cigarettes/day at time of stroke	*ND*	*ND*	*ND*	*ND*
Seoul (a)[35]	Pre	*NR*	Pre	*NR*	*NR*	Current smoking	> 7.5 units/day	*ND*	*ND*	*ND*
Seoul (b)[36]	Pre or post	160/90	Pre or post	Fasting > 6.1	*ND*	Current smoking	*ND*	> 5.7	*ND*	*ND*
Taiwan[37]	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	> 6.2	≥ 50%	Ultrasound, MRA or catheter angiography
Texas[38]	*NR*	*NR*	*NR*	*NR*	*ND*	*NR*	*ND*	ND	≥ 50%	Ultrasound

Table 3.3 (continued)

Study	Pre/post stroke	Cut-off (mm Hg)	Pre/post stroke	Cut off Fasting or random glucose (mmol/l)#	Ischaemic heart disease	Smoking	Alcohol‡	Raised cholesterol (mmol/l)¶	Cut-off	Method of measurement
USA (a)[39]	Pre	*NR*	Pre	*NR*	History of MI or angina	*ND*	*ND*	*ND*	*ND*	*ND*
USA (b)[40]	Pre	-	*NR*	*NR*	*NR*	Current smoking	≥ 4.5 units/day	On lipid-lowering medication	*ND*	*ND*

*Definitions for prior transient ischaemic attack and atrial fibrillation not shown.
† Values converted from mg/dl to mmol by multiplying by 0.055
‡ Values converted from grams into UK units where necessary (1unit = 8g)
¶ Values converted from mg/dl to mmol by multiplying by 0.02586
# Cut-off used when diabetes is defined according to blood glucose measurements post-stroke
ND = not determined; the risk factor concerned was either not studied or extractable data were not given in the publication(s); *NR* = not reported, even though the risk factor concerned was studied; MRA = magnetic resonance angiography

[1]Murat & Erturk 2002; [2]Vemmos *et al*. 2000; [3]Marti-Vilalta & Arbroix 1999; [4]Moulin *et al*. 2000; [5]Saposnick *et al*. 2000; [6]Saposnick *et al*. 2001; [7]Woo *et al*. 1999; [8]Pittock *et al*. 2002; [9]Mead *et al*. 1999; [10]Kolominsky-Rabas *et al*. 2001; [11]Grau *et al*. 2001; [12]Amarenco *et al*. 2006; [13]Aszalos *et al*. 2002; [14]Somay *et al*. 2006; [15]Kumral *et al*. 1998; [16]Kimura *et al*. 2004; [17]Bahou *et al*. 2004 ; [18]Sacco *et al*. 2006; [19]Tejada *et al*. 2003; [20]Hajat et al. 2001; [21]Norrving & Cronqvist 1989; [22]Lindgren *et al*. 1994; [23]Boiten & Lodder 1991; [24]Boiten *et al*. 1996; [25]Mead *et al*. 1998; [26]Liu *et al*. 2006; [27]Lodder *et al*. 1990; [28]Schulz *et al*. 2003; [29]Pinto *et al*. 2006; [30]Silvestrelli *et al*. 2006; [31]Awada & Rajeh 1999; [32]Petty *et al*. 1999; [33]Toni *et al*. 1995; [34]Rothrock *et al*. 1993; [35]Kim & Choi-Kwon 1999; [36]Lee *et al*. 2001; [37]Yip *et al*. 1997; [38]Tegeler *et al*. 1997; [39]Foulkes *et al*. 1998; [40]Ohira *et al*. 2006;

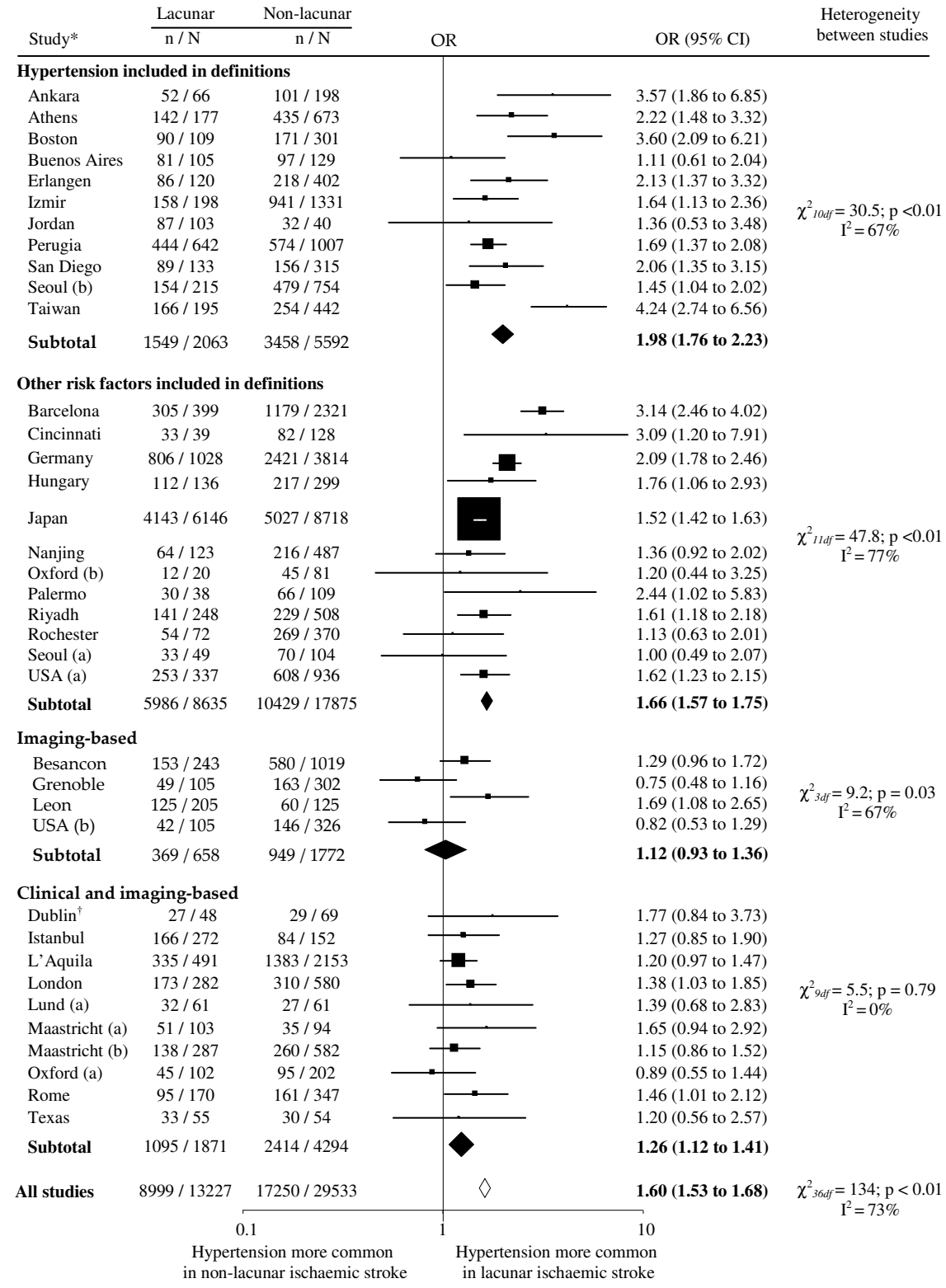
3.4.1 Hypertension

A total of 37 studies (42,760 patients, 13,227 with lacunar ischaemic stroke) presented data on hypertension. Of the 30 studies that reported a definition of hypertension, most defined it on the basis of raised blood pressure before or after the stroke (Table 3.3).

Overall, hypertension was commoner among patients with lacunar then non-lacunar ischaemic stroke (pooled OR 1.60, 95% CI 1.53 to 1.68). However, there was substantial heterogeneity between individual studies (I^2 = 73%), partly arising from the different methods used to define ischaemic stroke subtypes (Figure 3.2).

The excess of hypertension in patients with lacunar as compared with non-lacunar ischaemic stroke was most noticeable among studies in which the presence of hypertension favoured a diagnosis of lacunar ischaemic stroke, with an almost two-fold increase in the prevalence of hypertension among lacunar compared with non-lacunar patients (OR 1.98, 95% CI 1.76 to 2.23). Interestingly, this excess of hypertension was also present among studies that included risk factors other than hypertension when defining ischaemic stroke subtypes (OR 1.66, 95% CI 1.57 to 1.76). The increased prevalence of hypertension among those with lacunar ischaemic stroke was much less extreme (OR 1.26, 95% CI 1.12 to 1.41; Figure 3.2) in studies that used a clinical and imaging-based risk factor-free classification.

Figure 3.2 Odds ratios for hypertension (lacunar versus non-lacunar)

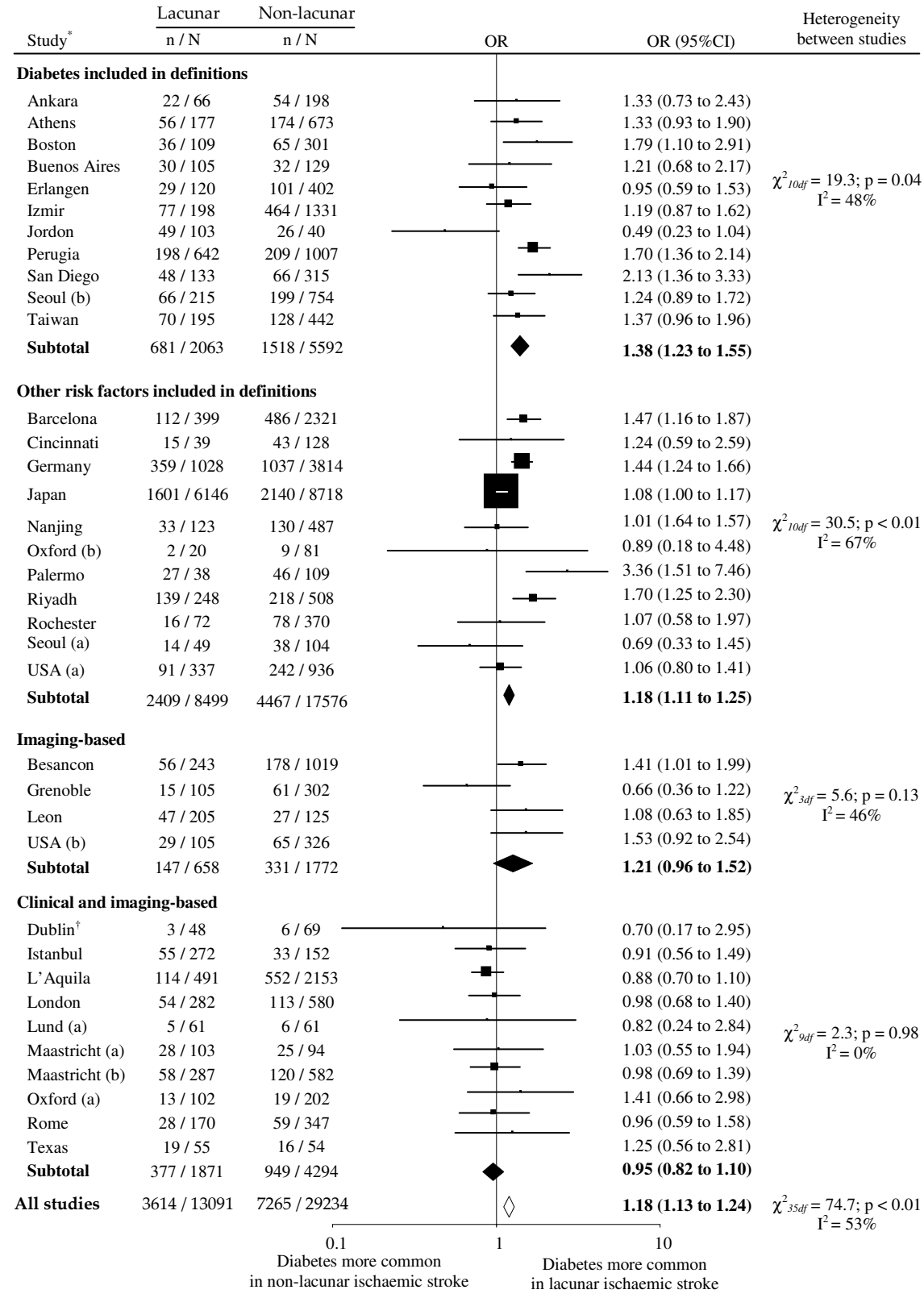


*For study references, refer to Table 3.1 (references included in footnotes to table)
†This study defined subtypes according to clinical syndrome only (not modified by brain imaging).
The diamond represents the overall pooled OR. N = total number of patients, n = number of patients with hypertension; OR = Odds ratio; CI = confidence interval. Heterogeneity between four groups: χ^2_{3df} = 40.6; p < 0.001.

3.4.2 Diabetes mellitus

Thirty-six studies (42,325 patients, 13,091 with lacunar ischaemic stroke) presented data on diabetes mellitus. Half of the studies gave a clear definition of diabetes, generally comprising a history of diabetes before or after the stroke or raised fasting blood glucose during admission (Table 3.3). Overall, diabetes appeared to be almost one fifth more common in patients with lacunar than non-lacunar ischaemic stroke (OR 1.18, 95% CI 1.13 to 1.24), but there was moderate heterogeneity between studies (Figure 3.3). However, when stratified by ischaemic stroke subtype classification method, this association was confined to those studies that used a classification method where diabetes favoured a definition of lacunar ischaemic stroke (OR 1.38, 95% CI 1.23 to 1.55), and among studies that included risk factors other than diabetes in the ischaemic subtype definitions (OR 1.18, 95% CI 1.11 to 1.25). Among studies using a risk factor-free classification, there was no difference in the prevalence of diabetes in patients with lacunar versus non-lacunar ischaemic stroke (pooled OR 0.95, 95% CI 0.82 to 1.10), with no heterogeneity between studies.

Figure 3.3 Odds ratios for diabetes (lacunar versus non-lacunar)



*For study references, refer to Table 3.1 (references included in footnotes to table)
†This study defined subtypes according to clinical syndrome only (not modified by brain imaging).
The open diamond represents the overall pooled OR. N = total number of patients, n = number of patients with diabetes; CI = confidence interval. Heterogeneity between four groups: $\chi^2_{3df} = 17.0$; $p < 0.001$.

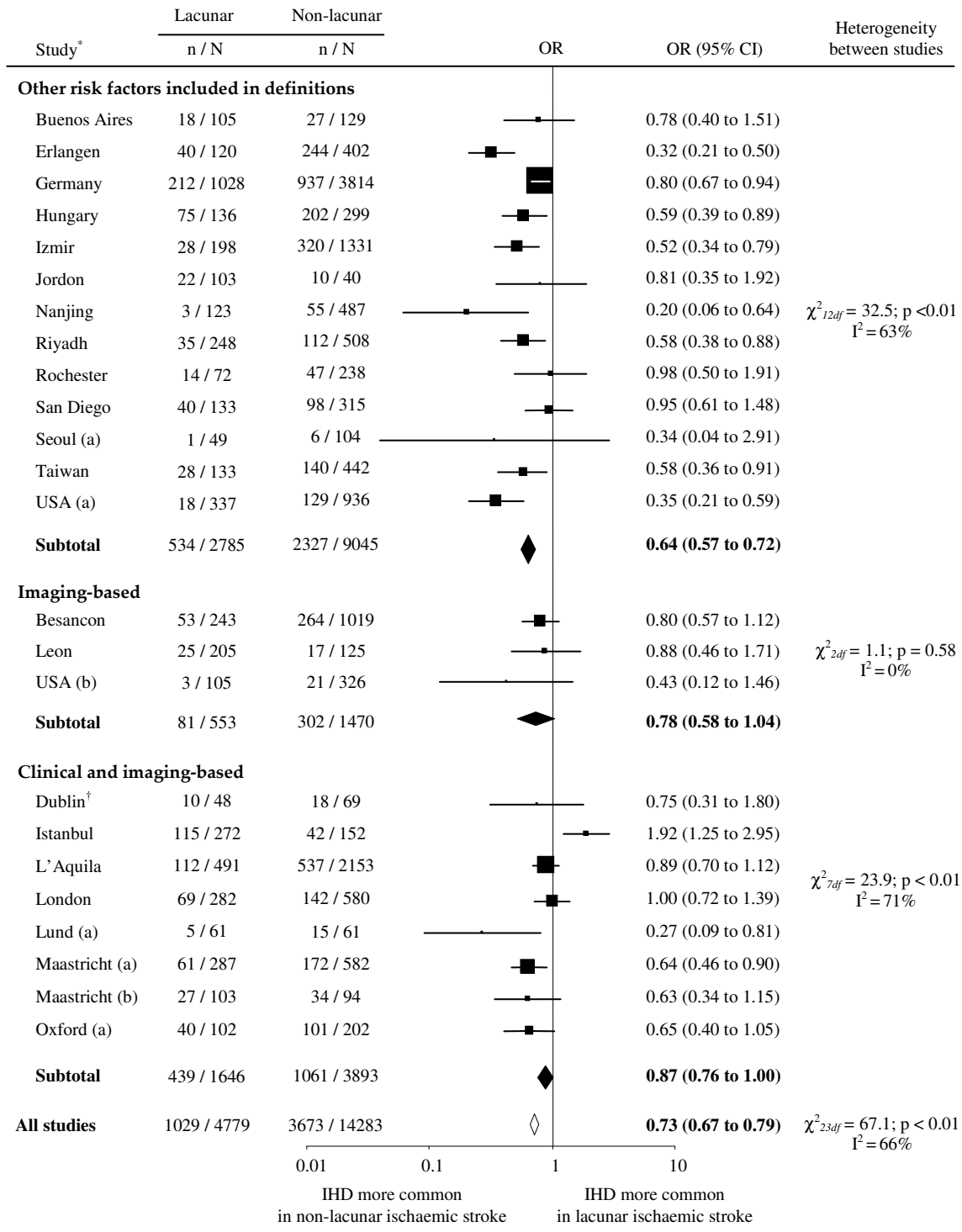
3.4.3 Ischaemic heart disease

24 studies (19,062 patients, 4779 with lacunar ischaemic stroke) presented data on IHD. Twelve studies gave a definition of IHD, most commonly defined as a history of myocardial infarction or angina. Overall IHD was significantly less frequent in lacunar than non-lacunar ischaemic stroke (pooled OR 0.73, 95% CI 0.67 to 0.79; Figure 3.4), although there was substantial heterogeneity between studies. The association was more extreme among studies that used a risk factor-based classification method (OR 0.64, 95% CI 0.57 to 0.72). However, among studies that used a factor-free classification method, the association was marginal, with an upper confidence limit compatible with no difference in prevalence of IHD between lacunar and non-lacunar ischaemic stroke (OR 0.87, 95% CI 0.76 to 1.00; Figure 3.4).

3.4.4 Atrial fibrillation

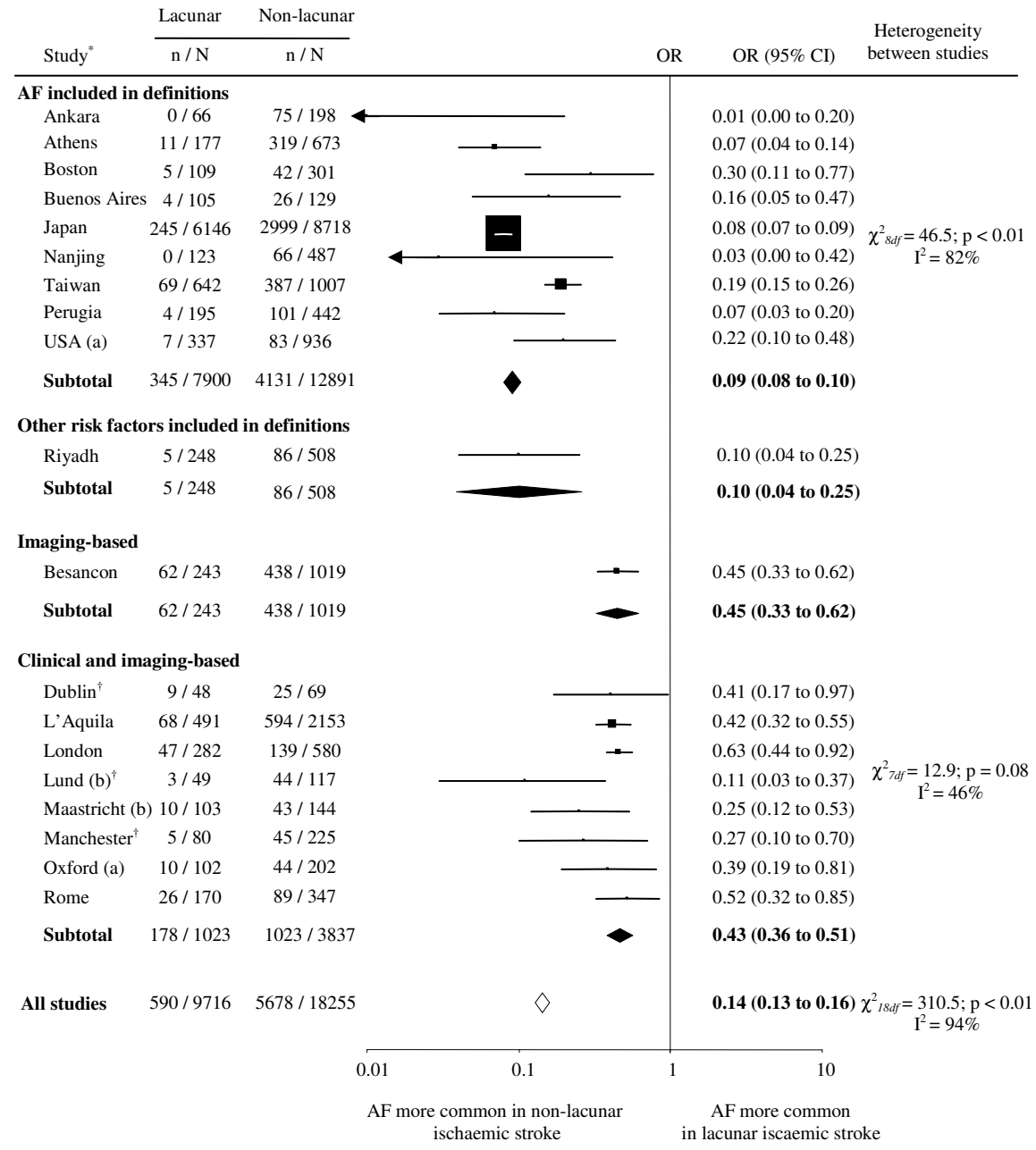
19 studies (27,971 patients, 9716 with lacunar ischaemic stroke), reported on prevalence of AF. Overall, AF was less common among patients with lacunar than non-lacunar ischaemic stroke (OR 0.14; 95% CI 0.13 to 0.16; Figure 3.5), but with substantial heterogeneity between studies. The association between AF and non-lacunar ischaemic stroke was particularly strong among studies in which the presence of AF favoured a diagnosis of non-lacunar ischaemic stroke (pooled OR 0.09, 95% CI 0.08 to 0.10), although there was substantial heterogeneity between studies (I^2 = 82%). The association was less extreme among studies using a clinical and imaging-based risk factor-free classification (OR 0.43, 95% CI 0.36 to 0.51), with moderate heterogeneity between studies.

Figure 3.4 Odds ratios for ischaemic heart disease (lacunar versus non-lacunar)



*For study references, refer to Table 3.1 (references included in footnotes to table)
†This study defined subtypes according to clinical syndrome only (not modified by brain imaging).
The open diamond represents the overall pooled OR. N = total number of patients, n = number of patients with IHD;
CI = confidence interval; IHD = ischaemic heart disease.
Heterogeneity between three groups: χ^2_{2df} = 9.6, p < 0. 01

Figure 3.5 Odds ratios for atrial fibrillation (lacunar versus non-lacunar)



*For study references, refer to Table 3.1 (references included in footnotes to table)
†These studies defined subtypes according to clinical syndrome only (not modified by brain imaging).
The open diamond represents the overall pooled OR. N = total number of patients, n = number of patients with AF; OR = odds ratio; CI = confidence interval; AF = atrial fibrillation.
Heterogeneity between 2 groups: $\chi^2_{1df} = 253.71$; $p < 0.001$

3.4.5 Carotid stenosis

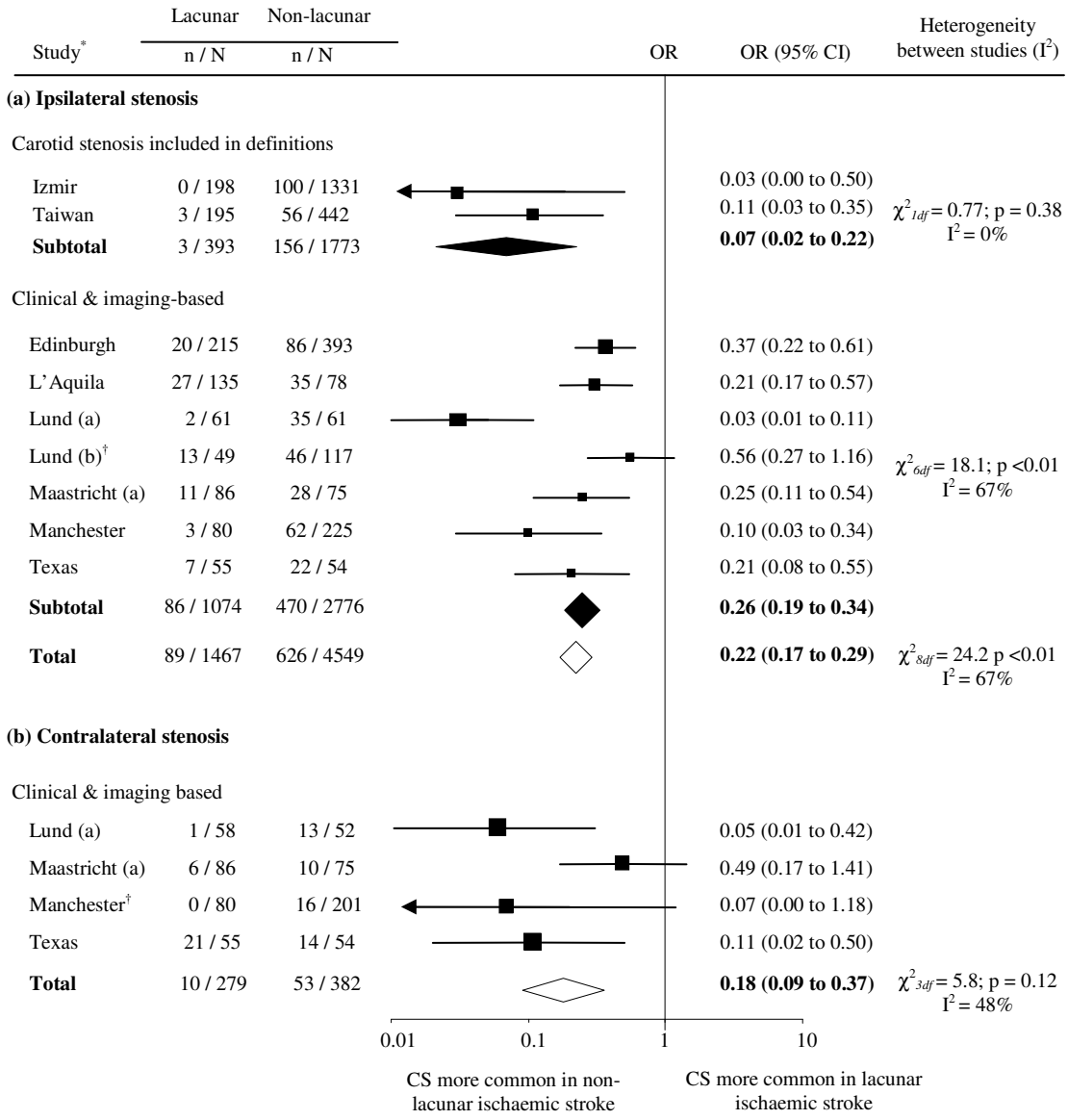
Nine studies (3850 patients, 1074 with lacunar ischaemic stroke) reported data on ipsilateral internal carotid artery (ICA) stenosis among stroke subtypes. Definitions of severe stenosis varied, but > 50% or > 70% ICA stenosis on ultrasound were the commonest (Table 3.3). Four of the studies also gave data on contralateral ICA stenosis. Overall there was a lower prevalence of ipsilateral carotid stenosis in patients with lacunar compared with non-lacunar ischaemic stroke (OR 0.22, 95% CI 0.17 to 0.29; Figure 3.6). However, this association was again more extreme among studies where severe stenosis favoured a definition of non-lacunar ischaemic stroke (pooled OR 0.07, 95% CI 0.02 to 0.22) and less pronounced among studies using clinical and imaging-based risk factor-free ischaemic subtype definitions (OR 0.26, 95% CI 0.19 to 0.34). The findings were similar for contralateral stenosis, where all studies were clinical and imaging-based (OR 0.18, 95% CI 0.09 to 0.37).

3.4.6 Smoking

Thirty-three studies (39,986 patients, 12,364 with lacunar ischaemic stroke) reported data on smoking. Overall, smoking was significantly more common among lacunar as compared with non-lacunar ischaemic stroke (pooled OR 1.21, 95% CI 1.15 to 1.28), although there was moderate heterogeneity between studies (Figure 3.7). This is a little surprising if the hypothesis that lacunar stroke is largely not due to atherosclerosis is indeed true, given the presumed pro-atherosclerotic properties of tobacco. I observed a similar result when I included only studies that used a clinical and imaging-based risk factor free classification method (pooled OR 1.12, 95% CI 0.98 to 1.28), although there was substantial heterogeneity between studies which

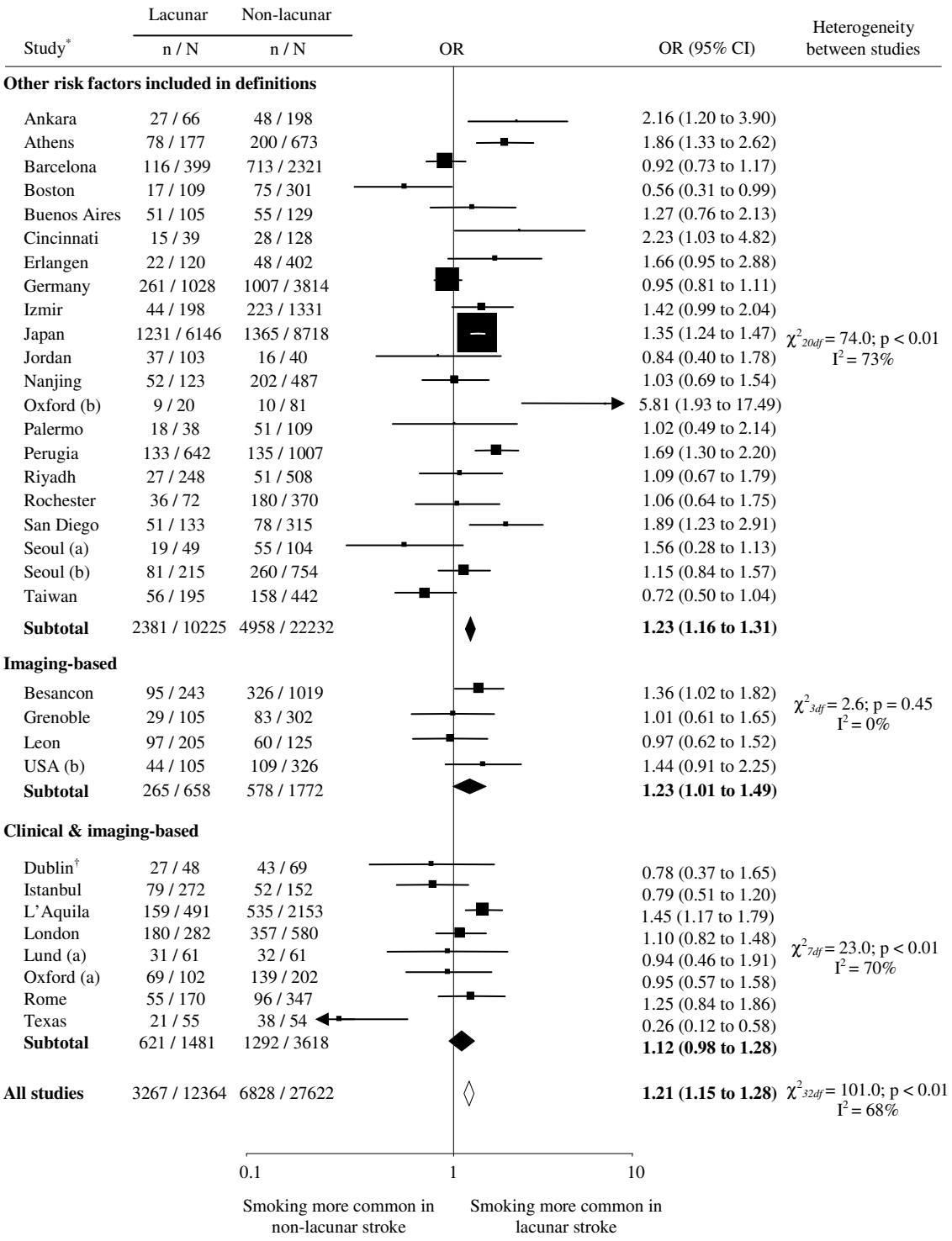
appeared to be mainly due to the results of one outlying study based in Texas (Tegeler *et al.* 1991).

Figure 3.6 Odds ratios for (a) ipsilateral carotid stenosis and (b) contralateral carotid stenosis (lacunar versus non-lacunar)



*For study references, refer to Table 3.1 (references included in footnotes to table)
†These studies defined subtypes according to clinical syndrome only (not modified by brain imaging).
The open diamond represents the overall pooled OR. N = total number of patients, n = number of patients with carotid stenosis; OR = odds ratio; CI = confidence interval; CS = carotid stenosis.
Heterogeneity between 2 groups for ipsilateral stenosis: $\chi^2_{1df} = 5.35$; $p < 0.01$

Figure 3.7 Odds ratios for smoking (lacunar versus non-lacunar)



*For study references, refer to Table 3.1 (references included in footnotes to table)
†This study defined subtypes according to clinical syndrome only (not modified by brain imaging).
The open diamond represents the overall pooled OR. N = total number of patients, n = number of patients exposed to smoking; OR = odds ratio; CI = confidence interval
Heterogeneity between 3 groups: $\chi^2_{2df} = 1.6$; p = 0.1

3.4.7 Raised cholesterol

Twenty studies (35,158 patients, 10,821 with lacunar ischaemic stroke) presented data on raised cholesterol. Overall raised cholesterol appeared to be more strongly associated with lacunar than non-lacunar ischaemic stroke (pooled OR 1.34, 95% CI 1.27 to 1.42; Figure 3.8), with substantial heterogeneity between studies ($I^2 = 56\%$). When only clinical and imaging-based studies were considered, there was a non-significant trend towards raised cholesterol being more common in lacunar ischaemic stroke (pooled OR 1.21, 95% CI 1.00 to 1.46).

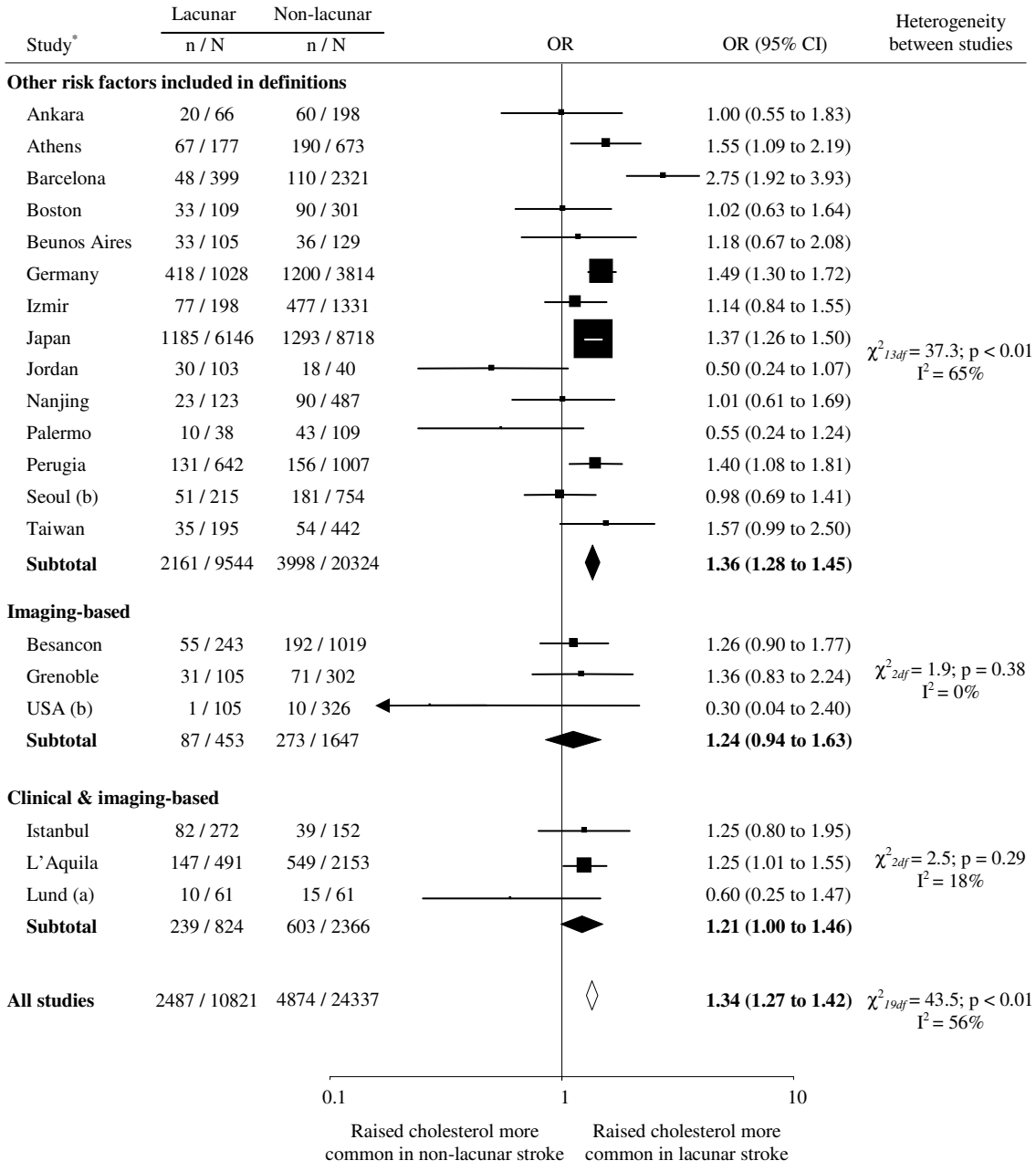
3.4.8 Previous TIA

Twenty-one studies (18,799 patients, 4628 with lacunar ischaemic stroke) presented data on previous TIA. There was no clear stronger association between previous TIA and either lacunar or non-lacunar ischaemic stroke, irrespective of the method used to classify ischaemic strokes subtypes (overall pooled OR 0.92, 95% CI 0.83 to 1.02; Figure 3.9). There was however moderate heterogeneity between studies that included TIA in the definition of ischaemic stroke subtypes, and substantial heterogeneity between studies that used risk factor-free clinical and imaging-based classification methods.

3.4.9 Alcohol Excess

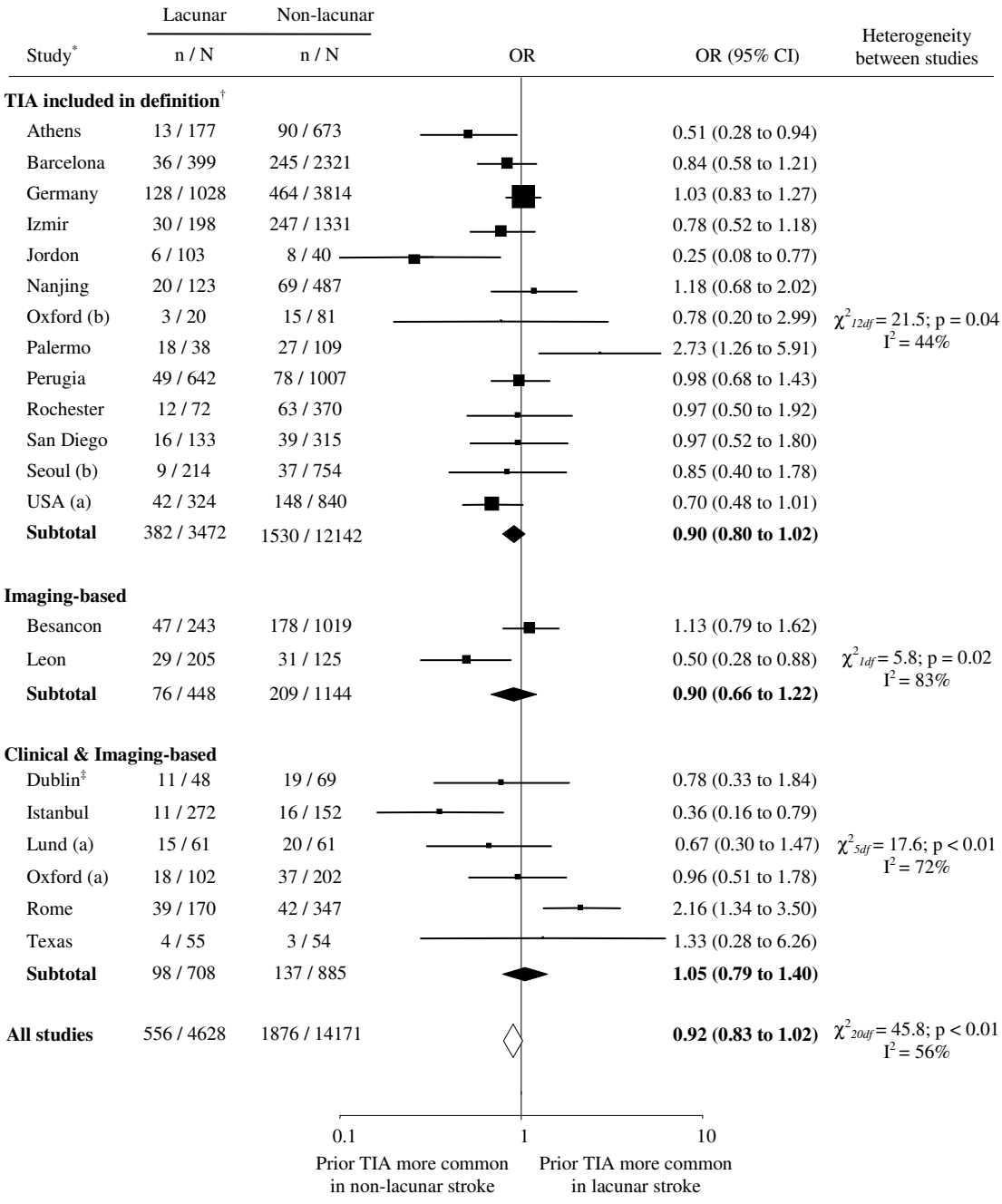
Thirteen studies (11,966 patients, 3419 with lacunar ischaemic stroke) presented data on alcohol excess. As with previous TIA, excess alcohol consumption did not appear to be more strongly associated with either lacunar or non-lacunar ischaemic stroke, irrespective of ischaemic stroke subtype classification method, with very little heterogeneity between studies overall (overall pooled OR 1.11, 95% CI 0.98 to 1.26; Figure 3.10).

Figure 3.8 Odds ratios for raised cholesterol (lacunar versus non-lacunar)



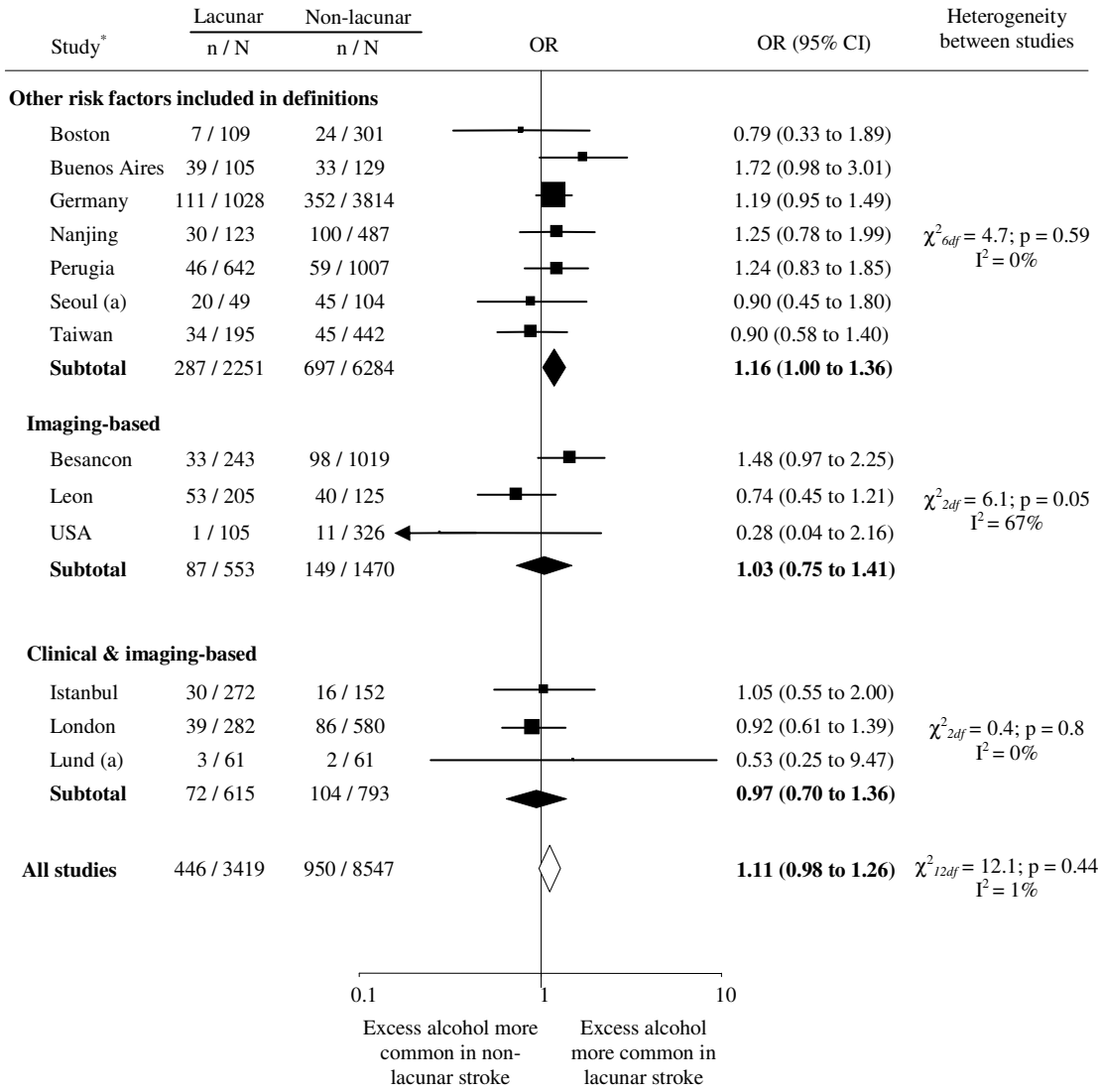
*For study references, refer to Table 3.1 (references included in footnotes to table)
The open diamond represents the overall pooled OR. N = total number of patients, n = number of patients with raised cholesterol; OR = odds ratio; CI = confidence interval
Heterogeneity between 3 groups: $\chi^2_{2df} = 1.82$; $p < 0.1$

Figure 3.9 Odds ratios for prior TIA (lacunar versus non-lacunar)



*For study references, refer to Table 3.1 (references included in footnotes to table)
†TIA included in definition of some non-lacunar ischaemic stroke subtypes
‡This study defined subtypes according to clinical syndrome only (not modified by brain imaging)
The open diamond represents the overall pooled OR. N = total number of patients, n = number of patients with prior TIA; OR = odds ratio; CI = confidence interval; TIA = transient ischaemic attack
Heterogeneity between 3 groups: χ^2_{2df} = 1.65; p < 0.1

Figure 3.10 Odds ratios for excess alcohol (lacunar versus non-lacunar)



*For study references, refer to Table 3.1 (references included in footnotes to table)
The open diamond represents the overall pooled OR. N = total number of patients, n = number of patients with history of excess alcohol; OR = odds ratio; CI = confidence interval
Heterogeneity between 3 groups: χ^2_{2df} = 0.98; p < 0.1

3.4.10 Sensitivity Analyses

When I excluded patients from the non-lacunar comparison group whose stroke was thought to be due to a cardiac source of emboli the results were generally similar to those of the primary analysis, although the summary odds ratio for each sub-group of studies was generally less extreme (Table 3.4). This may have been partly a consequence of reduced power, since fewer studies were included in the sensitivity analyses.

When I included only community-based studies and hospital-based studies that recruited from both inpatients and outpatients, the results were similar to those obtained in the primary analyses (Table 3.4).

Table 3.4 Sensitivity analyses showing summary odds ratios (lacunar vs non-lacunar) for (1) studies where cardioembolic strokes could be excluded from the non-lacunar comparison group and (2) only studies that are community-based, or hospital-based including both inpatients and outpatients

		Primary analysis		Cardioembolic strokes excluded from non-lacunar comparison group		Community-based studies or those recruiting inpatients and outpatients	
Risk factor	**Classification method**	**No. of studies / total patients / lacunar patients**	**OR (95% CI)**	**No. of studies / total patients / lacunar patients**	**OR (95% CI)**	**No. of studies / total patients / lacunar patients**	**OR (95% CI)**
Hypertension	HT included in definitions	11 / 7655 / 2063	1.98 (1.76 to 2.23)	11 / 5542 / 2063	1.80 (1.58 to 2.04)	2 / 970 / 253	2.10 (1.54 to 2.85)
	Other risk factors included	12 / 26510 / 8635	1.66 (1.57 to 1.75)	9 / 18892 / 1828	1.31 (1.22 to 1.39)	2 / 543 / 92	1.14 (0.69 to 1.89)
	Imaging-based	4 / 2430 / 658	1.12 (0.93 to 1.36)	1 / 431 / 105	2.05 (0.53 to 1.29)	2 / 761 / 310	1.17 (0.86 to 1.61)
	Clinical and imaging-based	10 / 6165 / 1871	1.26 (1.12 to 1.41)	3 / 428 / 219	1.45 (0.99 to 2.13)	4 / 3919 / 930	1.21 (1.03 to 1.41)
	Total	37 / 42760 / 13227	1.60 (1.53 to 1.68)	24 / 25293 / 10515	1.39 (1.31 to 1.47)	10 / 6193 / 1585	1.32 (1.16 to 1.41)
Diabetes	Diabetes included in definitions	11 / 7655 / 2063	1.38 (1.23 to 1.55)	11 / 5542 / 2063	1.13 (1.00 to 1.28)	2 / 970 / 253	1.44 (1.05 to 1.98)
	Other risk factors included	11 / 26075 / 8499	1.18 (1.11 to 1.25)	10 / 19342 / 8251	0.95 (0.89 to 1.02)	2 / 543 / 92	1.04 (0.59 to 1.85)
	Imaging-based	4 / 2430 / 658	1.21 (0.96 to 1.52)	2 / 756 / 210	1.27 (0.85 to 1.90)	2 / 761 / 310	1.29 (0.89 to 1.87)
	Clinical and imaging-based	10 / 6165 / 1871	0.95 (0.82 to 1.10)	3 / 428 / 219	1.06 (0.67 to 1.69)	3 / 3810 / 875	0.93 (0.77 to 1.12)
	Total	36 / 42325 / 13091	1.18 (1.13 to 1.24)	26 / 26068 / 10743	1.00 (0.94 to 1.05)	9 / 6084 / 1530	1.07 (0.93 to 1.24)

Table 3.4 continued

Risk factor	Classification method	Primary analysis		Cardioembolic strokes excluded from non-lacunar comparison group		Community-based studies or those recruiting inpatients and outpatients	
		No. of studies / total patients / lacunar patients	**OR (95% CI)**	**No. of studies / total patients / lacunar patients**	**OR (95% CI)**	**No. of studies / total patients / lacunar patients**	**OR (95% CI)**
Ischaemic heart disease	Other risk factors included	13 / 11830 / 2785	0.64 (0.57 to 0.72)	12 / 8540 / 2599	0.78 (0.69 to 0.88)	3 / 1280 / 325	0.60 (0.46 to 0.80)
	Imaging-based	3 / 2023 / 553	0.78 (0.58 to 1.04)	1 / 431 / 105	0.43 (0.12 to 1.46)	2 / 761 / 310	0.72 (0.41 to 1.27)
	Clinical and imaging-based	8 / 5539 / 1646	0.87 (0.76 to 1.00)	3 / 623 / 266	0.58 (0.40 to 0.82)	3 / 3810 / 875	0.88 (0.74 to 1.05)
	Total	24 / 19062 / 4779	0.73 (0.67 to 0.79)	16 / 9594 / 2970	0.75 (0.67 to 0.84)	8 / 5851 / 1510	0.78 (0.68 to 0.91)
Atrial fibrillation	AF included in definitions	9 / 20791 / 7900	0.09 (0.08 to 0.10)	8 / 15628 / 7834	0.58 (0.51 to 0.67)	-	-
	Other risk factors included in definitions	1 / 756 / 248	0.10 (0.04 to 0.25)	-	-	-	-
	Clinical and imaging-based	8 / 4860 / 1023	0.43 (0.36 to 0.51)	-	-	3 / 3810 / 875	0.47 (0.38 to 0.58)
	Total	19 / 27669 / 18255	0.14 (0.13 to 0.16)	8 / 15628 / 7834	0.58 (0.51 to 0.67)	3 / 3810 / 875	0.47 (0.38 to 0.58)

Table 3.4 continued

Risk factor	Classification method	Primary analysis		Cardioembolic strokes excluded from non-lacunar comparison group		Community-based studies or those recruiting inpatients and outpatients	
		No. of studies / total patients / lacunar patients	**OR (95% CI)**	**No. of studies / total patients / lacunar patients**	**OR (95% CI)**	**No. of studies / total patients / lacunar patients**	**OR (95% CI)**
Ipsilateral ICA stenosis	Stenosis included in definitions	2 / 2166 / 393	0.07 (0.02 to 0.22)	2 / 2642 / 393	0.12 (0.04 to 0.36)	-	-
	Clinical and imaging-based	7 / 3850 / 1074	0.26 (0.19 to 0.34)	-	-	3 / 930 / 405	0.32 (0.22 to 0.46)
	Total	9 / 6016 / 1467	0.22 (0.17 to 0.29)	2 / 2642 / 393	0.12 (0.04 to 0.36)	3 / 930 / 405	0.32 (0.22 to 0.46)
Contralateral ICA stenosis	Clinical and imaging-based	4 / 661 / 279	0.18 (0.09 to 0.37)	-	-	1 / 109 / 55	0.11 (0.02 to 0.50)
	Total	4 / 661 / 279	0.18 (0.09 to 0.37)	-	-	1 / 109 / 55	0.11 (0.02 to 0.50)
Smoking	Other risk factors included	21 / 32457 / 10225	1.23 (1.16 to 1.31)	20 / 23857 / 9977	0.97 (0.91 to 1.03)	4 / 1513 / 345	1.76 (1.35 to 2.30)
	Imaging-based	4 / 2430 / 658	1.23 (1.01 to 1.49)	-	-	-	-
	Clinical and imaging-based	8 / 5099 / 1481	1.12 (0.98 to 1.28)	2 / 231 / 116	1.98 (0.32 to 0.89)	-	-
	Total	33 / 39986 / 12364	1.21 (1.15 to 1.28)	22 / 24088 / 10093	0.96 (0.90 to 1.02)	4 / 1513 / 345	1.76 (1.35 to 2.30)

Table 3.4 continued

Risk factor	Classification method	Primary analysis		Cardioembolic strokes excluded from non-lacunar comparison group		Community-based studies or those recruiting inpatients and outpatients	
		No. of studies / total patients / lacunar patients	**OR (95% CI)**	**No. of studies / total patients / lacunar patients**	**OR (95% CI)**	**No. of studies / total patients / lacunar patients**	**OR (95% CI)**
Raised cholesterol	Other risk factors included	14 / 29868 / 9544	1.36 (1.28 to 1.45)	13 / 20372 / 8145	1.08 (1.01 to 1.15)	-	-
	Imaging-based	3 / 410 / 109	1.24 (0.94 to 1.63)	-	-	1 / 431 / 105	0.30 (0.04 to 2.40)
	Clinical and imaging-based	3 / 3190 / 824	1.21 (1.00 to 1.46)	-	-	1 / 2644 / 491	1.25 (1.01 to 1.55)
	Total	20 / 35158 / 10821	1.34 (1.27 to 1.42)	13 / 20372 / 8145	1.08 (1.01 to 1.15)	1 / 431 / 105	0.30 (0.04 to 2.40)
Prior TIA	Prior TIA included in definitions	13 / 15614 / 3472	0.90 (0.80 to 1.02)	13 / 11767 / 3435	0.79 (0.70 to 0.90)	3 / 991 / 225	0.95 (0.61 to 1.46)
	Imaging-based	2 / 1592 / 448	0.90 (0.66 to 1.22)	-	-	1 / 330 / 205	0.50 (0.28 to 0.88)
	Clinical and imaging-based	6 / 1593 / 708	1.05 (0.79 to 1.40)	2 / 231 / 116	0.82 (0.49 to 1.40)	2 / 413 / 157	1.00 (0.56 to 1.78)
	Total	21 / 18799 / 4628	0.92 (0.83 to 1.02)	15 / 11998 / 3551	0.82 (0.74 to 0.91)	6 / 1734 / 587	0.81 (0.60 to 1.09)
Alcohol excess	Other risk factors included	7 / 8535 / 2251	1.16 (1.00 to 1.36)	7 / 6248 / 2251	1.03 (0.88 to 1.21)	-	-
	Imaging-based	3 / 2023 / 553	1.03 (0.75 to 1.41)	-	-	2 / 761 / 310	0.68 (0.43 to 1.09)
	Clinical and imaging-based	3 / 1408 / 615	0.97 (0.70 to 1.36)	1 / 122 / 61	1.53 (0.25 to 9.47)	1 / 862 / 282	0.92 (0.61 to 1.39)
	Total	13 / 11966 / 3419	1.11 (0.98 to 1.26)	8 / 6370 / 2312	1.03 (0.88 to 1.21)	3 / 1623 / 592	0.81 (0.59 to 1.10)

HT = hypertension; OR = odds ratio; CI = confidence interval; AF = atrial fibrillation; IHD = ischaemic heart disease; ICA = internal carotid artery; TIA = transient ischaemic attack

3.5 Discussion

Many studies have examined the association of risk factors with different ischaemic stroke subtypes. Their pooled results must be interpreted with some caution, with careful consideration of the potential sources of heterogeneity between studies.

3.5.1 Ischaemic stroke subtype classification bias

The most important and striking difference between studies identified in my systematic review was the classification method used to assign ischaemic stroke subtypes. Many studies included the risk factors under investigation in their definitions of ischaemic stroke subtypes, which may have led to bias (hereafter referred to as "classification bias") when assessing differences in risk factor profiles of lacunar versus non-lacunar ischaemic stroke. The subtype classification method used when investigating risk factor-ischaemic stroke subtype associations should be free of aetiological assumptions about risk factors, and so ideally should be based solely on the clinical features of the stroke syndrome along with the site and size of any relevant lesion on brain imaging.

Classification bias was of particular importance in the results for hypertension and diabetes. The apparently stronger association between hypertension and lacunar as compared with non-lacunar ischaemic stroke was considerably attenuated when only studies using risk factor-free classification methods were considered, whilst the apparent excess of diabetes among patients with lacunar versus non-lacunar ischaemic stroke disappeared entirely.

Classification bias also affected the results for AF, carotid stenosis and IHD. The excess of AF and carotid stenosis among non-lacunar patients was (unsurprisingly) more extreme among studies in which the presence of AF or carotid stenosis

precluded or discouraged a diagnosis of lacunar ischaemic stroke. Emboli from the heart can occasionally occlude small, perforating cerebral vessels, and so it may be difficult to ascertain whether AF is causal or simply a manifestation of generalised vascular disease. Similarly, although carotid stenosis is much more prevalent among patients with non-lacunar ischaemic stroke, it does occur in association with some lacunar ischaemic strokes. IHD was overall significantly less common among patients with lacunar than non-lacunar ischaemic stroke, although, again this association was attenuated (and not quite statistically significant) when only studies using a risk factor-free classification method were considered. A history of IHD is generally not included in definitions of ischaemic stroke subtypes where the classification takes into account risk factors, although a history of myocardial infarction within four weeks prior to the stroke occurrence may allow a patient to be categorised under "cardioembolic stroke" in aetiological classifications (Adams *et al*. 1993; Whisnant *et al*. 1990).

It is interesting that classification methods that do not include the risk factor being studied in their ischaemic stroke subtype definitions but do include other risk factors in those definitions, also yield more extreme estimates of the association between the risk factor and lacunar versus non-lacunar ischaemic stroke. This could reflect associations between risk factors.

3.5.2 Variation between studies in stroke population studied

Another potential source of variability between studies is in the population of patients studied. Most studies identified were hospital-based. An ideal study would include all strokes that occurred in the community in a defined geographical area, irrespective of whether or not they attended hospital. One meta-analysis of

community-based studies comparing risk factor profiles of different ischaemic stroke subtypes found just four such studies (Schulz & Rothwell 2003), all of which have been included in this review. Such community-based studies should avoid spurious differences in risk factor profiles between ischaemic stroke subtypes arising because of hospital admission selection bias. However, such studies will be prone to other potential biases. Diagnosis of ischaemic stroke depends on appropriately timed brain imaging to exclude intracerebral haemorrhage, and patients managed entirely outwith hospital are unlikely to access such imaging. Additionally, subtyping of ischaemic stroke patients is less accurate in the absence of brain imaging. Thus, a series of patients recruited from outpatients as well as hospital admissions is unlikely to be any more biased than a community-based register. Indeed, the results of my primary analyses were essentially unchanged in a sensitivity analysis restricted to only those studies that were based in the community or included both inpatient admissions and outpatients.

3.5.3 Variable misclassification of ischaemic stroke subtypes

A further potential source of variation between studies using risk factor-based classification methods such as TOAST is the reliance on a number of investigations (such as carotid ultrasound, transcranial doppler, echocardiography etc) apart from brain imaging, access to which will vary considerably between countries and centres, and according to patient characteristics such as age. Furthermore, the TOAST classification does not allow assignment of an ischaemic stroke subtype when there is more than one potential cause of stroke, which in one large hospital-based stroke register occurred in 7% of all ischaemic strokes (Moncayo *et al*. 2000). In this case, or in the case of incomplete investigation or complete investigation without detection

of cause, patients are categorised as "undetermined aetiology". In the studies that used the TOAST classification, the proportion of patients in this category varied widely from 8% to 41% (Lee *et al*. 2001; Saposnik *et al*. 2001). This must be partly due to variability in access to diagnostic investigations but probably also reflects inconsistent application of the TOAST criteria (Goldstein *et al*. 2001). The large and variable proportion of patients in the "undetermined" subtype category (some of which will be lacunar, and others non-lacunar, in unknown proportions) introduces heterogeneity between studies. A classification that can assign a stroke subtype to all (or almost all) ischaemic stroke patients in the study population will be less prone to such variability, favouring classifications based mainly on clinical features of stroke syndrome, preferably refined by brain imaging findings.

However, even if all ischaemic strokes are assigned a subtype, there will still inevitably be some misclassification. Although combining the findings on brain imaging with clinical features of the stroke syndrome will help to minimise this misclassification, a proportion of ischaemic strokes will remain misclassified. In particular, about 10-20% of lacunar infarcts will be misclassified as small cortical infarcts and vice versa (Mead *et al*. 1999a) because the clinical features of the stroke syndrome alone are sometimes of limited accuracy in distinguishing between these subtypes, and sometimes the relevant infarct is not visible on CT or MR brain scan. The extent of the misclassification in the studies included in this analysis will depend partly on the proportion of patients with brain imaging and the type and timing of imaging used, which varied between the included studies. Small recent infarcts are more likely to be seen with diffusion-weighted MR brain imaging, but none of the studies I identified reported using this technique. The effects of misclassification of

subtypes on the risk factor associations in my meta-analysis are difficult to predict, and will depend on whether misclassification is independent of exposure status. Some studies have demonstrated that up to around one third of stroke patients with lacunar syndromes have patterns of multiple areas of infarction on DW MR brain imaging, which is perhaps suggestive of some lacunar strokes being due to an underlying atherothromboembolic pathology, as opposed to a distinct small vessel pathology (Caso *et al*. 2005; Wessels *et al*. 2005; Ay *et al*. 1999). However, given that it is difficult to distinguish between acute and subacute lesions on DW MR imaging (Caso *et al*. 2005), we cannot be sure whether the multiple infarcts observed in these studies occurred at the same time rather than within a few weeks of each other. Nonetheless, it is possible that some lacunar strokes may be caused by atherothromboembolism. I therefore addressed this issue in my systematic review by performing a sensitivity analysis where I excluded those patients with presumed cardioembolic stroke from the comparison groups. Interestingly, the results did not differ from those in the primary analyses. As discussed in chapter 7, I was able to explore this issue further in my analyses of individual patient data from various stroke registers, by further refining the classification of the lacunar comparison group to take into account the presence of severe carotid stenosis as well as cardiac sources of emboli.

3.5.4 Variable definitions of risk factors

Variability in the definitions used for the risk factors studied could also account for some of the heterogeneity between results of different studies. For some risk factors, such as hypertension, whether or not the definition is dependent on pre-stroke or post-stroke criteria will impact on the proportion of patients classed as having been

exposed to that risk factor. This in turn may lead to differences in risk factor-ischaemic stroke subtype associations, although the precise effect of particular definitions on risk factor associations is, again, unpredictable.

Also, misclassification of risk factors through dichotomisation of continuous variables, such as hypertension, may have biased risk factor-ischaemic stroke subtype relationships. The precise effect of this bias will depend on whether this misclassification is independent of outcome status. In addition, the use of "crude" definitions, which fail to distinguish between subcategories of exposure, may have obscured any true associations between such subcategories and ischaemic stroke subtype. Also, the duration and severity of exposure to risk factors, particularly hypertension and diabetes, as well as the effect of combined exposure to multiple risk factors may all impact on each risk factor-ischaemic stroke subtype relationship.

One of the limitations of my meta-analysis is that I was able to determine univariate associations only, since individual patient data would be needed for multivariate modelling. I was therefore unable to adjust for the confounding effects of age, sex and other risk factors.

3.5.5 Conclusion

The results of my systematic review and meta-analysis suggest that the apparent stronger association between diabetes and lacunar compared with non-lacunar ischaemic stroke may arise almost entirely from classification bias. Similarly, the stronger association between hypertension and lacunar versus non-lacunar ischaemic stroke was largely due to effects of classification bias, although a marginal excess of hypertension amongst patients with lacunar ischaemic stroke was still observed in studies free from such bias. Although important risk factors for ischaemic stroke in

general, the presence of diabetes, and probably hypertension, do not help to distinguish the ischaemic stroke subtype. In addition, although AF and carotid stenosis are associated more with non-lacunar than lacunar ischaemic stroke, this association is less extreme in studies free from classification bias than in studies using risk factor-based classification methods. IHD may similarly be slightly less common in lacunar than non-lacunar ischaemic stroke, whereas smoking and raised cholesterol may be more common in lacunar than non-lacunar ischaemic stroke. However as described, these findings are limited by the various shortcomings of many of the included studies and a lack of control for the confounding effects of age, sex and other vascular risk factors. These issues are addressed in chapter 7, where I report the results of my analysis of risk factor-ischaemic stroke subtype associations in a large collaborative individual patient data pooling project. I will therefore discuss the implications of the differences in risk factor profiles of different ischaemic stroke subtypes on our understanding of the arteriopathy of lacunar ischaemic stroke in more detail in this later chapter.

Chapter 4. Risks of death and recurrent vascular events in patients with lacunar versus non-lacunar ischaemic stroke: a systematic review and meta-analysis

4.1 Aim

In this chapter I will present the findings from my systematic review and meta-analysis of published studies reporting on risks of death, recurrent stroke and/or myocardial infarction, and on recurrent stroke subtype patterns, among patients with lacunar as compared with non-lacunar ischaemic stroke, to determine whether differences in prognosis provide evidence for a distinct lacunar arteriopathy.

4.2 Introduction

Lacunar ischaemic stroke is often thought to have a more favourable outcome than other ischaemic stroke subtypes. Short term prognosis for death and disability is better among patients with lacunar compared with non-lacunar ischaemic stroke (Norrving 2003), but this may reflect smaller infarct size and a low early recurrence rate rather than a fundamentally different arterial pathology. In the longer term, patients with lacunar ischaemic stroke have a significantly higher risk of death than the general population (Norrving 2003), but less is known about the difference in risk of death between patients with lacunar and non-lacunar stroke.

Similarly, early recurrent stroke risk is lower in patients with lacunar ischaemic stroke compared with other ischaemic stroke subtypes (Lovett 2004). This early difference probably reflects different arterial occlusive mechanisms, with non-lacunar ischaemic stroke more likely to be caused by emboli from an active

thrombotic source, such as the carotid bifurcation or the heart. However, it does not necessarily imply fundamentally different arterial pathologies, since atherothrombotic mechanisms *in situ* could still cause most lacunar stroke. Reports on recurrent stroke risk in the longer term are conflicting. Some studies have found that the risk of recurrence is greater among patients with non-lacunar than lacunar ischaemic stroke while others suggest that stroke subtype is not a predictor of stroke recurrence (Norrving 2003). These inconsistencies may arise from differences in study methodology and small study size (specifically small numbers of recurrent events). Furthermore, the definition of recurrent stroke differs markedly between studies, particularly with respect to the minimum time required to have passed between the index stroke and the recurrence. This makes comparing studies difficult, and may explain why estimates of the early recurrence risk differ so much between studies (Coull & Rothwell 2004).

It is often assumed that ischaemic stroke subtypes "breed true", in that the subtype of recurrent stroke is generally of the same subtype as the index event. If true, this may support the hypothesis of a distinct underlying arterial pathology in lacunar ischaemic stroke. If most lacunar ischaemic stroke is due to a non-atherosclerotic pathology, we might also expect the risk of myocardial infarction (MI), a marker of systemic atherothrombotic disease, to be lower among patients with lacunar stroke. I therefore carried out a systematic review and series of meta-analyses of cohort studies that followed patients with lacunar and non-lacunar ischaemic stroke for death, recurrent stroke and / or MI. I compared risks of death and recurrent stroke and examined data on recurrent stroke subtype patterns and MI risk following lacunar compared with non-lacunar ischaemic stroke.

4.3 Methods

4.3.1 Study identification

I sought cohort studies that had followed both lacunar and non-lacunar ischaemic stroke patients for at least one month for death, recurrent stroke and/or MI. I identified relevant studies published in English language journals between January 1966 and September 2007 inclusive through a comprehensive electronic search strategy using Medline and Embase (Appendices 3 and 4); perusing reference lists of all relevant primary and review articles identified; searching within books on cortical and subcortical stroke; and discussions with colleagues. I included inception cohort studies that were either community or hospital-based, but excluded studies among highly selected groups of patients (e.g. clinical trials or studies of young patients only) and studies that were not inception cohorts. I also excluded studies that met the initial inclusion criteria but were found to have irresolvable data inconsistencies.

4.3.2 Data extraction

From each study identified, I extracted data on:

- the population studied (i.e. community or hospital-based, hospital admissions only or including outpatients, consecutive recruitment or not)
- the numbers of patients with lacunar and non-lacunar ischaemic stroke (excluding those with unusual causes of ischaemic stroke, e.g. arterial dissection, hereditary causes of stroke such as CADASIL, etc)
- the demographic characteristics of the study population
- the definition of recurrent stroke
- the stroke subtype classification method
- the duration of follow up

- the proportion of patients with brain imaging following index and recurrent stroke
- the numbers of lacunar and non-lacunar ischaemic stroke patients who were dead or had a recurrent stroke at one month, from 1-12 months, and from 1-5 years after the index stroke
- the numbers of lacunar and non-lacunar patients who had an MI
- the numbers and subtypes of recurrences among patients with lacunar and non-lacunar stroke at baseline.

I chose one month, 1-12 month, and 1-5 year time periods for death and recurrent stroke because this allowed separate assessment of the very early and longer term risks for these outcomes in the maximum number of studies. It also eliminated the effects of varying definitions of early stroke recurrence in the assessment of longer term risk.

4.3.3 Statistical analysis

I calculated risks of death and recurrent stroke at 1 month, 1-12 months and 1-5 years with 95% confidence intervals (CIs) using Confidence Interval Analysis software (Bryant 2000).

For studies with data on death and recurrent stroke I calculated study-specific and summary Peto odds ratios (non-lacunar versus lacunar ischaemic stroke) with 95% CIs for each of death and recurrent stroke at 1 month, 1-12 months and 1-5 years, using Cochrane Review Manager software (Cochrane Collaboration 2003). I assessed heterogeneity between studies using the I^2 statistic which loosely describes heterogeneity as mild ($I^2 < 30$), moderate ($30 > I^2 < 50$) or substantial ($I^2 > 50$) (Higgins & Thompson 2002).

4.3.3.1 Sensitivity analyses

In sensitivity analyses, I repeated the analyses for death and recurrent stroke including community-based studies (or studies that had recruited from both inpatients and outpatients) only.

4.3.3.2 Recurrent stroke subtype patterns

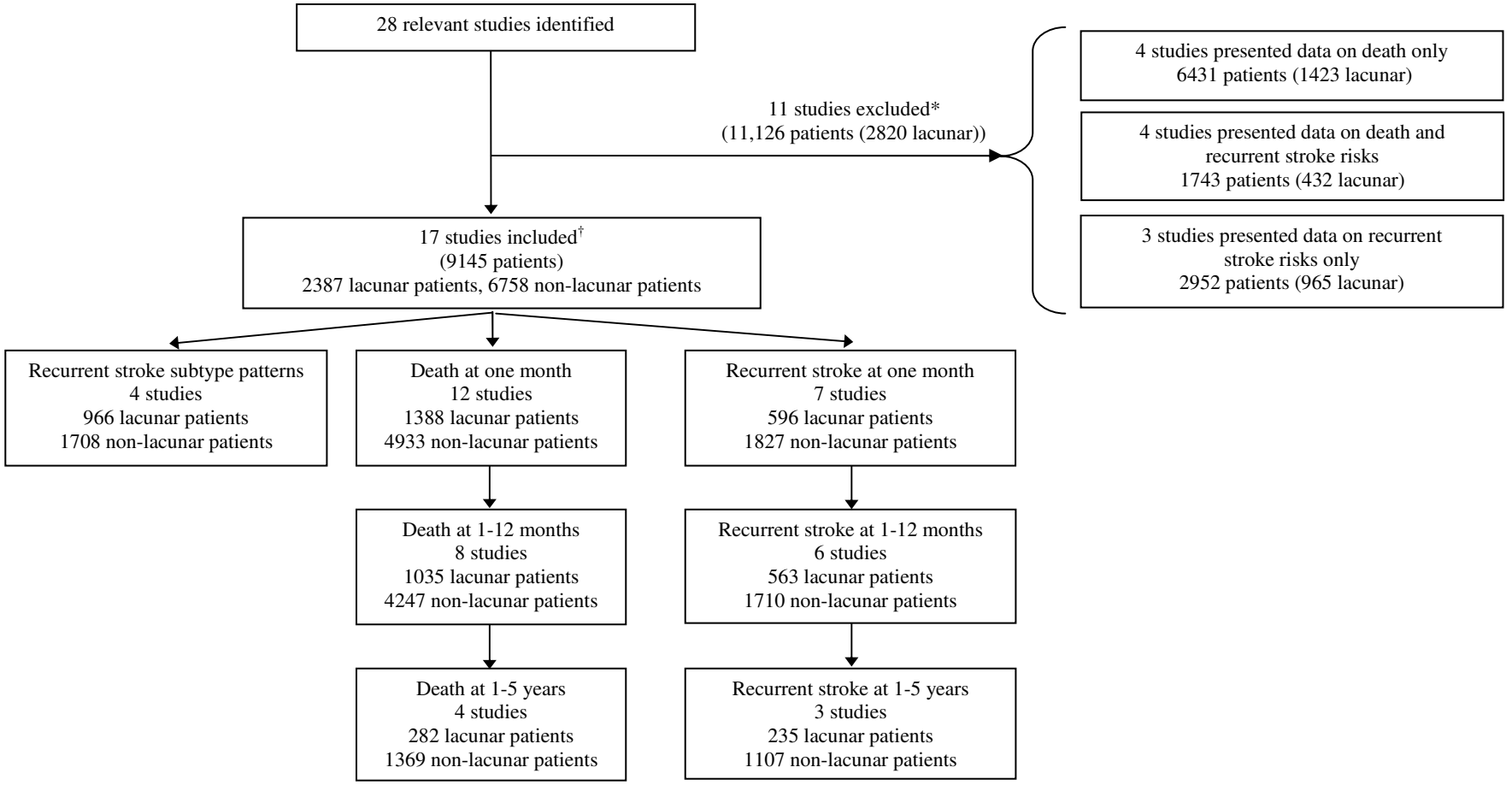
I analysed data on recurrent stroke subtypes using three different methods:

1) I pooled data from all relevant studies to determine the proportions of patients with lacunar and non-lacunar ischaemic stroke (at baseline) with each type of recurrent stroke
2) I pooled data from all studies providing information on recurrent stroke subtypes, and calculated study-specific and summary odds ratios (ORs) of having a lacunar recurrence or of having a non-lacunar recurrence (for lacunar versus non-lacunar ischaemic stroke at baseline)
3) I determined the ratio of the observed proportion of lacunar recurrences following a lacunar index event to the proportion expected (24%), and the ratio of the observed to the expected proportion (54%) of non-lacunar recurrences following a non-lacunar index event (with expected proportions based on two community-based studies of first-ever stroke incidence (Bamford *et al*. 1991; Hillen *et al*. 2003)).

4.4 Results

My search initially identified 5267 abstracts. Reading these revealed 126 potentially relevant studies, of which 28 were actually relevant. Data on one or more outcome were extractable from 17 (9145 patients, 2387 lacunar ischaemic stroke) of these 28 studies (Figure 4.1).

Figure 4.1 Flow diagram detailing number of studies with extractable data for each outcome



*Details of excluded studies and their main findings are given in Table 4.1.
†Some studies included data on both death and recurrent stroke, so overlap means that the number of studies in the first three boxes below this level do not add up to 17

4.4.1 Details of excluded studies

I was unable to extract and include data from 11 studies (11,126, 2820 lacunar ischaemic stroke) (Figure 4.1). Of these 11 studies, four (6431 patients, 1423 lacunar strokes) reported data on death only, and contributed over half of the total number of patients in all excluded studies. One of these studies was particularly large (4842 patients), but followed patients for just 3 months and did not report on death at one month (Grau *et al*. 2001). Two studies followed patients for 1 year, but there were irresolvable data inconsistences in one (Brainin *et al*. 1992), and data were not extractable from the other (Liu *et al*. 2005). In the fourth study, patients were followed for two years, but again data were not extractable (Giroud *et al*. 1991) (Table 4.1). Four studies presented data on both death and recurrent stroke (1743 patients, 432 lacunar strokes). In two of these studies patients were followed for just 6 months, and data at one month were not reported (Murat & Erturk 2002; Pittock *et al*. 2003). Data were not extractable from the other two studies, in which patients were followed for 2 years (Kolominsky-Rabas *et al*. 1998) and 1 year (Soda *et al*. 2004).

Three studies reported data on recurrent stroke only (2952 patients, 965 lacunar ischaemic strokes). One of these studies followed patients for only 3 months, and did not present any data at one month post-stroke (Moroney et al. 1998), one study followed patients for two years, but presented the data in an unextractable format (Hier *et al*. 1991), and one study followed patients for 10 years, but also presented the data in an unextractable format (Yokota et al. 2004).

Of the 7 studies that reported data on recurrent stroke, one was community-based (Kolominsky-Rabas *et al*. 1998) and the remainder were hospital-based.

Table 4.1 Details of studies that were relevant but excluded from analyses

Study	Year	Stroke population recruited	Length of follow-up (months)	Total patients included (lacunar patients)	Reason for exclusion	Outcomes reported	Key findings reported
Austria[1]	1992	Admissions to hospital (first-ever stroke)	12	365 (107)	Irresolvable data inconsistencies	Death	• Patients with a lacunar ischaemic stroke had a lower 1-year mortality rate compared with all other ischaemic stroke subtypes
Dijon[2]	1991	Community-based	24	614 (165)	Data not extractable	Death	• Patients with a lacunar ischaemic stroke had a lower 2-year mortality rate compared with other ischaemic stroke subtypes
Germany[3]	2001	Admissions to hospital (multicentre)	3	4842 (1028)	Reported outcome data at 3 months only	Death	• Proportion of patients dead at 3 months was lowest in the lacunar group, compared with all other ischaemic stroke subtypes
Nanjing[4]	2006	Admissions to hospital (first-ever stroke)	12	610 (123)	Did not report one month outcome data	Death	• There was a statistically significant difference in mortality rate between ischaemic stroke subtypes, with the mortality rate lowest in patients with lacunar ischaemic stroke
Dublin[5]	2003	Consecutive admissions to hospital	6	117 (48)	Reported outcome data at 3 weeks and 6 months only	Death "stroke extension" and "stroke/ TIA"[†]	• Proportion of patients dead at 6 months was greater in the non-lacunar than lacunar group • A greater proportion of patients with non-lacunar than lacunar ischaemic stroke had a "stroke extension" at two weeks, but there was no difference in risk at six months[†] • There was no difference in the proportion of patients with stroke/TIA between ischaemic stroke subtypes at 2 weeks, but a greater proportion of non-lacunar than lacunar patients had a stroke/TIA at 6 months[†]

Table 4.1 continued

Study	Year	Stroke population recruited	Length of follow-up (months)	Total patients included (lacunar patients)	Reason for exclusion	Outcomes reported	Key findings reported
Erlangen[6]	2001	Community-based	24	531 (120)	Data not extractable	Death	• Ischaemic stroke subtype significantly predicted death at two years, with the lowest rate of death amongst patients with lacunar ischaemic stroke
						Recurrent stroke	• Ischaemic stroke subtype was not found to be a predictor of long-term recurrence at 2 years
Japan[7]	2004	Admissions to hospital (multicentre)	12	829 (198)	Data not extractable	Death	• The proportion of patients who died during follow-up was lowest in the lacunar group compared with other ischaemic stroke subtype groups
						Recurrent stroke	• There was no difference in rate of recurrent stroke at 1 year between ischaemic stroke subtypes
Turkey[8]	2002	Consecutive admissions to neurology department	6	266 (66)	Reported outcome data at 6 months only	Death	• Mortality rate at 6 months was lower among lacunar compared with other ischaemic stroke subtypes
						Recurrent stroke	• There was no statistically significant difference in risk of recurrent stroke at 6 months between ischaemic stroke subtypes

Table 4.1 continued

Study	Year	Stroke population recruited	Length of follow-up (months)	Total patients included (lacunar patients)	Reason for exclusion	Outcomes reported	Key findings reported
Osaka[9]	2004	Consecutive admissions to stroke unit (first-ever stroke)	120	1382 (556)	Data not extractable	Recurrent stroke	• The rate of recurrence was statistically significantly higher among cardioembolic stroke patients than lacunar patients during the first year. The recurrence rate also appeared to be higher among patients with atherothrombotic strokes compared with lacunar stroke, but the statistical significance of this was not reported. • After the first year, the recurrence rate was not significantly different between stroke subtypes
USA[10]	1991		24	1273 (337)	Outcome data not extractable	Recurrent stroke	• The rate of recurrent stroke at 30-days was greater among patients with atherothrombotic compared with lacunar ischaemic stroke, but it is unclear from the author's report whether there was a difference in recurrence rate thereafter
USA (b)[11]	1998	Admissions to hospital	3	297 (72)	Reported outcome data at 3 months only	Recurrent stroke	• Recurrence risk at 3 months was statistically significantly lower among patients with lacunar ischaemic stroke compared with patients with atherothrombotic or cardioembolic strokes

*of publication. †Authors of the Dublin study did not define what they meant by "stroke extension" and how this differed from the outcome of "stroke/TIA"
TIA = transient ischaemic attack
[1]Brainin *et al*. 1992; [2]Giroud *et al*. 1991; [3]Grau *et al*. 2001; [4]Liu *et al*. 2005; [5]Pittock *et al*. 2003; [6]Kolominsky-Rabas *et al*. 2001; [7]Soda *et al*. 2004; [8]Murat & Erturk 2002; [9]Yokota *et al*. 2004; [10]Hier *et al*. 1991; [11]Moroney *et al*. 1998

4.4.2 Characteristics of included studies

Characteristics of the remaining 17 studies contributing to the analyses are shown in Table 4.2 (Lavados *et al*. 2007; Hata *et al*. 2005; Sacco *et al*. 2006; Hillen *et al*. 2003; Boiten & Lodder 1993; De Jong *et al*. 2004; Landi *et al*. 1992; Sacco *et al*. 1994; Bamford *et al*. 1991; Lovett *et al*. 2004; Pinto *et al*. 2006; Anderson *et al*. 1994; Sacco *et al*. 1991; Petty *et al*. 2000; Toni *et al*. 1995; Eriksson & Olsson 2001; Nadeau *et al*. 1993).

In 14 of these 17 studies, the non-lacunar comparison group consisted of all non-lacunar ischaemic strokes. One study excluded patients with subtentorial ischaemic stroke from the non-lacunar group (Toni *et al*. 1995), one excluded patients with cardioembolic ischaemic stroke (Nadeau *et al*. 1993), and a third excluded patients with a posterior circulation stroke or a cardioembolic stroke (Boiten & Lodder 1993).

Thirteen studies reported the proportion of patients with brain imaging after their baseline stroke, which ranged from 74% to 100%, with four studies using MR imaging in addition to CT brain imaging. In one study, 37% of baseline strokes had CT or MR brain imaging, but many of the patients without brain imaging had an autopsy performed, resulting in 92% of baseline strokes having had brain imaging or autopsy (Hata *et al*. 2005).

Table 4.2 Description of included studies

Study	Year[*]	Stroke population recruited	Mean age		Male (%)		Follow up (months) (% loss)	Patients with CT/MRI brain scan (%)		Total patients included[#] (lacunar patients)	Outcome data extracted[†]
			Lacunar	Non-lacunar	Lacunar	Non-lacunar		Index stroke	Recurrent stroke		
Chile[1]	2007	Community-based (first-ever stroke)	64	68	63	53	6 (1)	NR	NA	184 (57)	D
Hisayama[2]	2005	Population-based	NR	NR	NR	NR	120 (0)	37% had CT or MRI[‡]	40% had CT or MRI[‡]	298 (167)	RSS
L'Aquila[3]	2006	Community-based (first-ever stroke)	73	75	51	46	60 (0)	100% had CT or MRI	NA	2644 (491)	D
London[4]	2003	Community-based (first-ever stroke)	NR	NR	NR	NR	14 (0)	87% had CT or MRI	65% had CT or MRI	1166 (401)	RSS
Maastricht (a)[5]	1993	Admissions of first-ever stroke to hospital, excluding subtentorial infarcts	67	70	55	63	Max 29 (0)	93% had CT	56% had CT	197 (103)	D, R
Maastricht (b)[6]	2004	As in Maastricht (a)	NR	NR	NR	NR	Mean 23 (NR)	100% had CT	61% had CT	998 (339)	RSS
Milan[7]	1992	Patients seen in ER within 72 hrs of first-ever stroke & admitted to neurology dept	64	66	63	61	Mean 28 (0)	100% had CT	NR	191 (88)	D, R, MI

Table 4.2 (continued)

Study	Year*	Stroke population recruited	Mean age		Male (%)		Follow up (months) (% loss)	Patients with CT/MRI brain scan (%)		Total patients included# (lacunar patients)	Outcome data extracted†
			Lacunar	Non-lacunar	Lacunar	Non-lacunar		Index stroke	Recurrent stroke		
New York[8]	1994	Hospitalised first-ever strokes who were residents of Northern Manhattan	NR	NR	NR	NR	Mean 40 (6)	NR	NR	306 (85)	D, R
Oxford (a)[9]	1991	Community-based (first-ever strokes)	72	73	40	54	12 (0)	93% had CT	NR	543 (137)	D, R
Oxford (b)[10]	2004	Community-based (first-ever strokes)	NR	NR	NR	NR	12 (NR)	NR	NR	150 (33)	R
Palermo[11]	2006	Consecutive admissions to internal medicine and cardioangiology departments	61	62	58	58	1 (NR)	100% had CT	NA	147 (38)	D
Perth[12]	1994	Community-based (first-ever strokes)	NR	NR	NR	NR	12 (0)	76% (of entire cohort) had CT	NA	247 (22)	D
Rochester (a)[13]	1991	Community-based (first-ever strokes)	NR	NR	NR	NR	60 (NR)	NR	NR	594 (78)	D, R

Table 4.2 (continued)

Study	Year*	Stroke population recruited	Mean age		Male (%)		Follow up (months) (% loss)	Patients with CT/MRI brain scan (%)		Total patients included[#] (lacunar patients)	Outcome data extracted[†]
			Lacunar	Non-lacunar	Lacunar	Non-lacunar		Index stroke	Recurrent stroke		
Rochester (b)[14]	2000	Community-based (first-ever strokes)	73	76	43	40	Mean 38 (0)	92% had CT, MRI (or autopsy)	NR	442 (72)	D, R
Rome[15]	1995	Consecutive first-ever stroke patients admitted within 12 hours of onset of event	67	68	65	55	1 (0)	100% had CT	NA	517 (170)	D
Sweden[16]	2001	Admissions to stroke unit	71	73	55	43	168 (0)	74% had CT	NA	309 (47)	D
USA[17]	1993	Consecutive admissions to the Veterans Administration Medical Centre	NR	NR	100	100	Median 36 (7)	100% had CT	NR	212 (59)	RSS

*of publication
[†]D = data on death; R = data on recurrent stroke; RSS = data on recurrent stroke subtypes; MI = data on frequency of MI following ischaemic stroke subtypes; MRI = magnetic resonance imaging; CT = computed tomography
[‡]In this study many of the patients had an autopsy and the authors report that 92% of index strokes and 94% of recurrences had either brain imaging or autopsy performed.
[#]Number of patients recruited at baseline, and not necessarily equal to the number of patients included in later analyses.

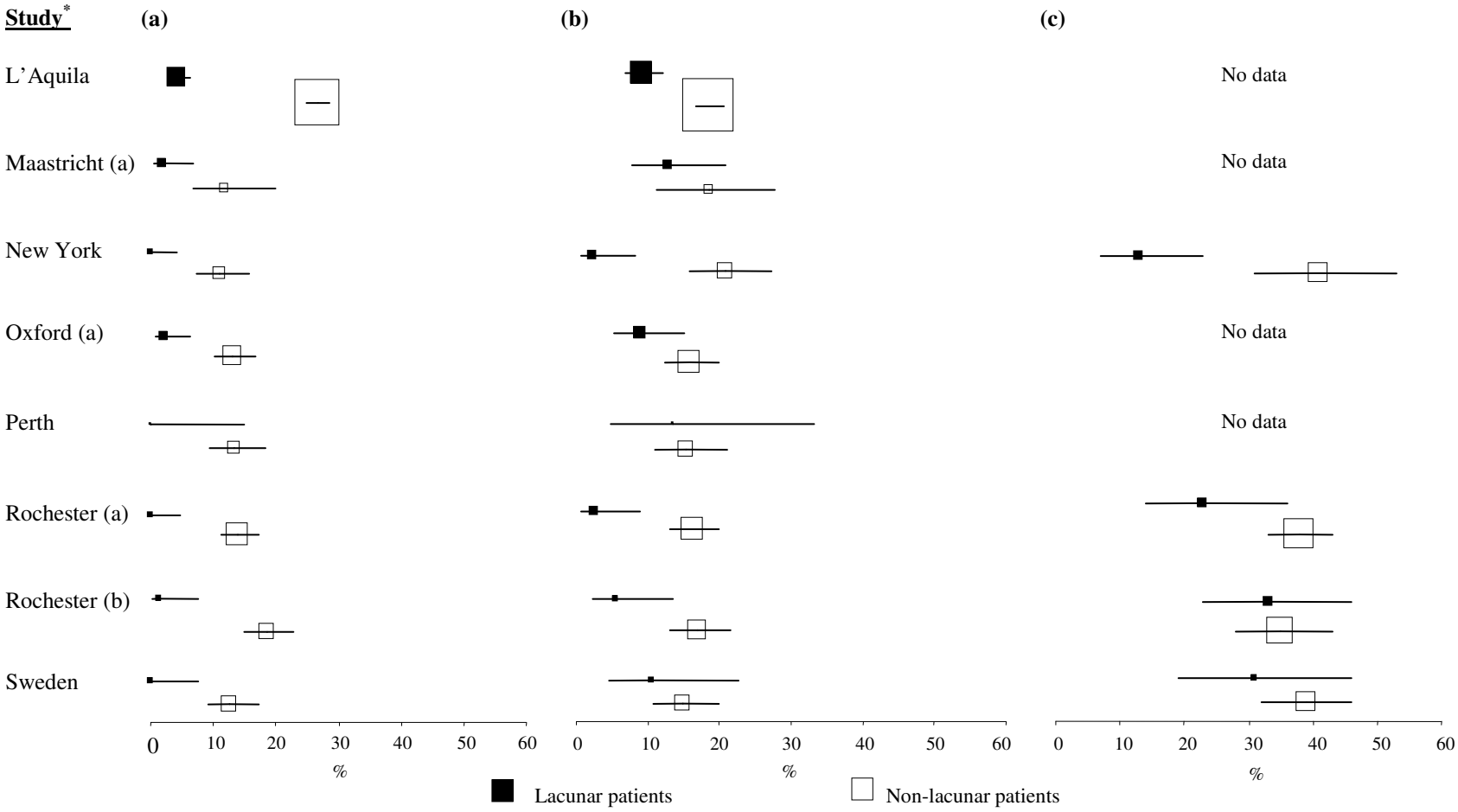
[1]Lavados *et al*. 2007; [2]Hata *et al*. 2005; [3]Sacco *et al*. 2006; [4] Hillen *et al.* 2003; [5] Boiten & Lodder, 1993; [6] De Jong *et al*. 2004; [7] Landi *et al*. 1992; [8] Sacco *et al*. 1994; [9] Bamford *et al.* 1991; [10]Lovett *et al*. 2004 ; [11]Pinto *et al*. 2006; [12] Anderson *et al*. 1994; [13] Sacco *et al.* 1991; [14] Petty *et al*. 2000; [15] Toni *et al*. 1995; [16] Eriksson & Olsson 2001; [17] Nadeau *et al*. 1993

4.4.3 Death

Of the 8 studies (5282 patients, 1035 lacunar strokes) reporting on death in lacunar and non-lacunar patients at both 1 month and 1 year (Anderson *et al*. 1994; Bamford *et al*. 1991; Boiten & Lodder 1993; Eriksson & Olsson 2001; Petty *et al*. 2000; Sacco *et al*. 1994; Sacco *et al*. 2006; Sacco *et al*. 1991), all but one included first-ever strokes only and five were community-based.

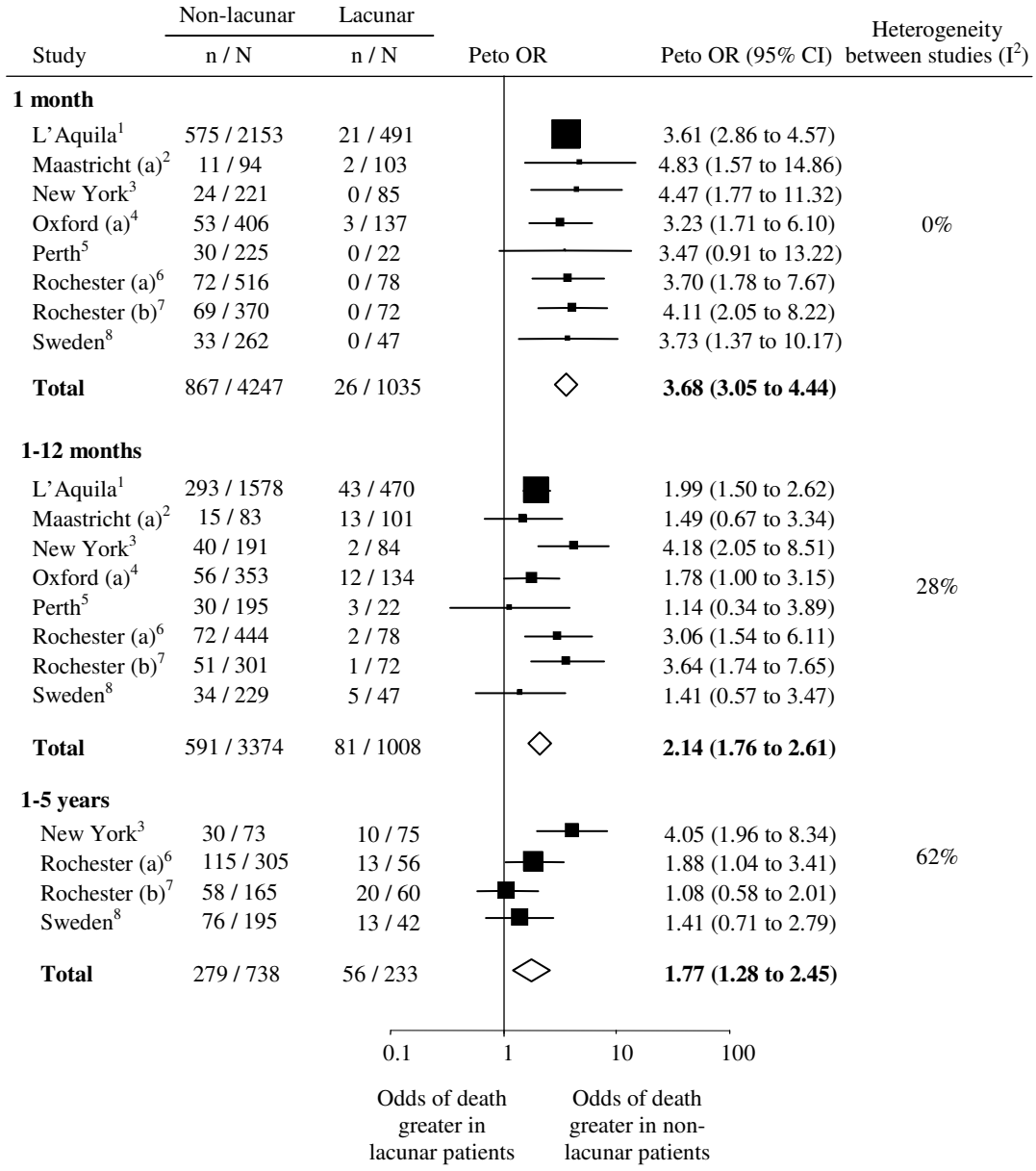
The risk of death among lacunar patients ranged from 0% to 4% at 1 month, 2% to 14% at 1-12 months, and 13% to 33% at 1-5 years. Among non-lacunar patients, the risk of death was higher at one month, ranging from 11% to 27%, while at 1-12 months the risk ranged from 15% to 21% and at 1-5 years, 35% to 41% (Figure 4.2). At one month the odds of death were over three and a half-fold greater in non-lacunar than lacunar patients (OR 3.68, 95% CI 3.05 to 4.44; Figure 4.3). This difference attenuated thereafter, with the odds of death at 1-12 months just two-fold greater among non-lacunar patients (OR 2.14, 95% CI 1.76 to 2.61), and at 1-5 years less than two-fold greater among non-lacunar patients (OR 1.77, 95% CI 1.28 to 2.45). However, there was moderate heterogeneity between studies for the 1-5 year results. Data for this later time period are less reliable, since they were only available for four studies (Eriksson & Olsson 2001; Petty *et al*. 2000; Sacco *et al*. 1994; Sacco *et al*. 1991) in 1651 patients, and their extraction required assumptions to be made about losses to follow-up and the statistical methods used in the original studies. In the studies included in these mortality analyses, the lacunar patients were very slightly younger than the non-lacunar patients (weighted mean age 72 versus 75 years), but I was unable to control for the potential confounding effect of this age difference in my analyses.

Figure 4.2 Risks of death with 95% CIs at (a) 1 month, (b) 1-12 months and (c) 1-5 years among lacunar and non-lacunar patients



*For study references, see Table 4.1 (references to studies included in footnotes to table)

Figure 4.3 Odds ratios of death at 1 month, 1-12 months and 1-5 years, comparing non-lacunar versus lacunar ischaemic stroke



N = total number of patients; n = number of deaths. OR = odds ratio; CI = confidence interval.
Squares represent the individual study-specific odds ratio estimates (with size of square reflecting weighting) with the vertical lines representing the 95% CI. Open diamonds represent the overall pooled ORs.

[1]Sacco *et al*. 2006; [2]Boiten & Lodder 1993; [3]Sacco *et al*. 1994; [4]Bamford *et al*. 1991; [5]Anderson *et al*. 1994; [6]Sacco *et al*. 1991; [7]Petty *et al*. 2000; [8]Eriksson & Olsson 2001

As described earlier, I was unable to include data from 8 relevant studies that reported on risk of death, the follow-up time having ranged from 3-24 months. These studies reported on death for the entire period for which patients were followed up and found risk of death to be lower among patients with lacunar versus other ischaemic stroke subtypes (Table 4.1) (Brainin *et al*. 1992; Giroud *et al*. 1991; Grau *et al*. 2001; Liu *et al*. 2005; Pittock *et al*. 2003; Kolominsky-Rabas *et al*. 2001; Soda *et al*. 2004; Murat & Erturk) . Although these studies did not distinguish between risk of death at early and later time periods, these results are not in disagreement with those from studies included in my meta-analysis.

4.4.4 Recurrent stroke

Of the 17 studies included in my analyses, 7 studies reported data on recurrent stroke risk at one month or more (2423 patients, 596 with lacunar strokes) (Bamford *et al*. 1991; Boiten *et al*. 1993; Landi *et al*. 1992; Petty *et al*. 2000; Sacco *et al*. 1994; Sacco *et al*. 1991; Lovett *et al*. 2004). Four of these studies were community-based and all included first-ever strokes only (Table 4.2). In each study the proportion of index strokes with brain imaging was close to 100%. The proportion of patients with a recurrent stroke with brain imaging performed was reported in only one study, in which 56% of recurrent stroke patients had a CT scan (Boiten *et al*. 1993). Studies presenting data on recurrent stroke risk used either a risk factor-independent clinical and brain imaging-based method of classifying ischaemic stroke subtypes, or a classification method that took into account the presence or absence of some risk factors, but not hypertension or diabetes, (i.e. NINDS classification or a modified TOAST classification) (Table 4.3). Three studies gave a definition of recurrent stroke (Bamford *et al*. 1991; Petty *et al*. 2000; Lovett *et al*. 2004), one study made no

distinction between their definition of index and recurrent stroke (Sacco *et al*. 1994), two studies gave no definition of a recurrent stroke (Landi *et al*. 1992; Sacco *et al*. 1991), and one study gave no definition but reported no recurrent strokes in either group within the first month, suggesting that the authors may have used a definition of recurrent stroke that excluded events occurring within a month of the index event (Boiten *et al*. 1993) (Table 4.3).

Table 4.3 Details of ischaemic stroke subtype classification method and definition of recurrent stroke in studies of recurrent stroke risk

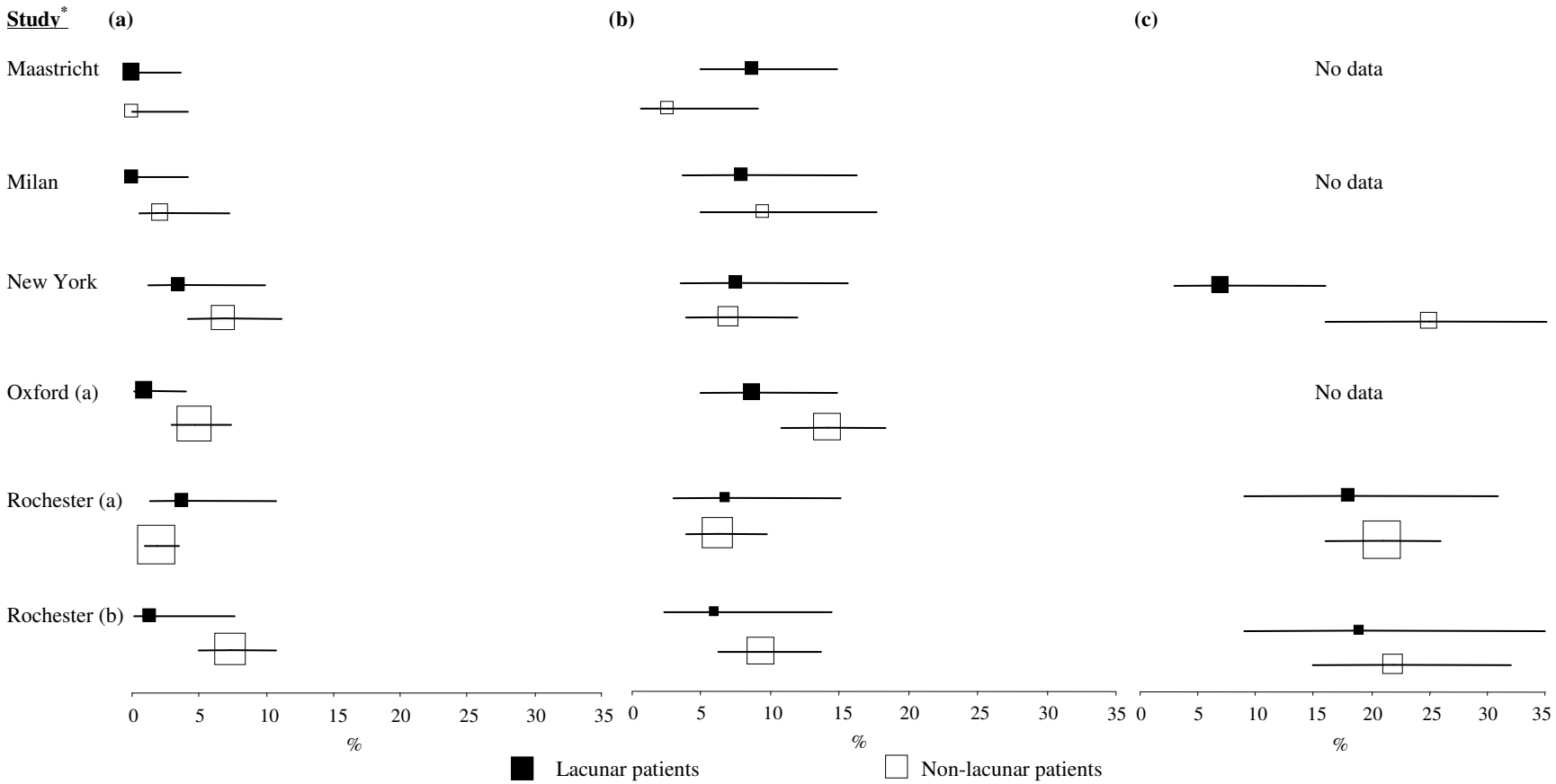
Study	Ischaemic stroke subtype classification	Definition of recurrent stroke
Maastricht (a)[1]	Risk factor-free (clinical syndrome and brain imaging-based)	Not reported
Milan[2]	Unclear	Not reported
New York[3]	Risk factor-based (NINDS)	Defined using standard definition of stroke
Oxford (a)[4]	Risk factor-free (clinical syndrome, not modified by brain imaging)	Standard stroke definition, with added criteria that side effects of drug therapy or intercurrent illness were excluded as potential explanations for any new neurological worsening, and recurrences within 21 days of the index stroke had to occur in a different part of the brain from the index event
Oxford (b)[5]	Modified TOAST	Standard stroke definition, with added critera that oedema, haemorrhagic transformation, intercurrent illness or iatrogenesis were excluded as potential causes of any new neurological worsening, and recurrences defined as occurring after a period of neurological stability lasting at least 24 hours
Rochester (a)[6]	Risk factor-free (clinical syndrome and brain imaging-based)	Not reported
Rochester (b)[7]	Risk factor-based (NINDS)	Standard stroke definition, with added critera that oedema, haemorrhagic transformation, intercurrent illness or iatrogenesis were excluded as potential causes of any new neurological worsening, and recurrences defined as occurring after a period of neurological stability lasting at least 24 hours

[1]Boiten & Lodder; [2]Landi *et al*. 1992; [3]Sacco *et al*. 1994; [4]Bamford *et al*. 1991; [5]Lovett *et al*. 2004; [6]Sacco *et al*. 1991; [7]Petty *et al*. 2000

Six of these seven studies reported data on recurrent stroke risk at both 1 month and 12 months. The risk of recurrence among lacunar patients during the first month ranged from 0% to 4% and at 1-12 months from 6% to 9%. The risk of recurrence at 1-5 years varied considerably between the three studies with long-term data, ranging from 7% to 22%. Among non-lacunar patients the one month recurrence risk ranged from 0% to 7%, the 1-12 month risk ranged from 3% to 14% and the 1-5 year risk ranged from 21% to 25% (Figure 4.4).

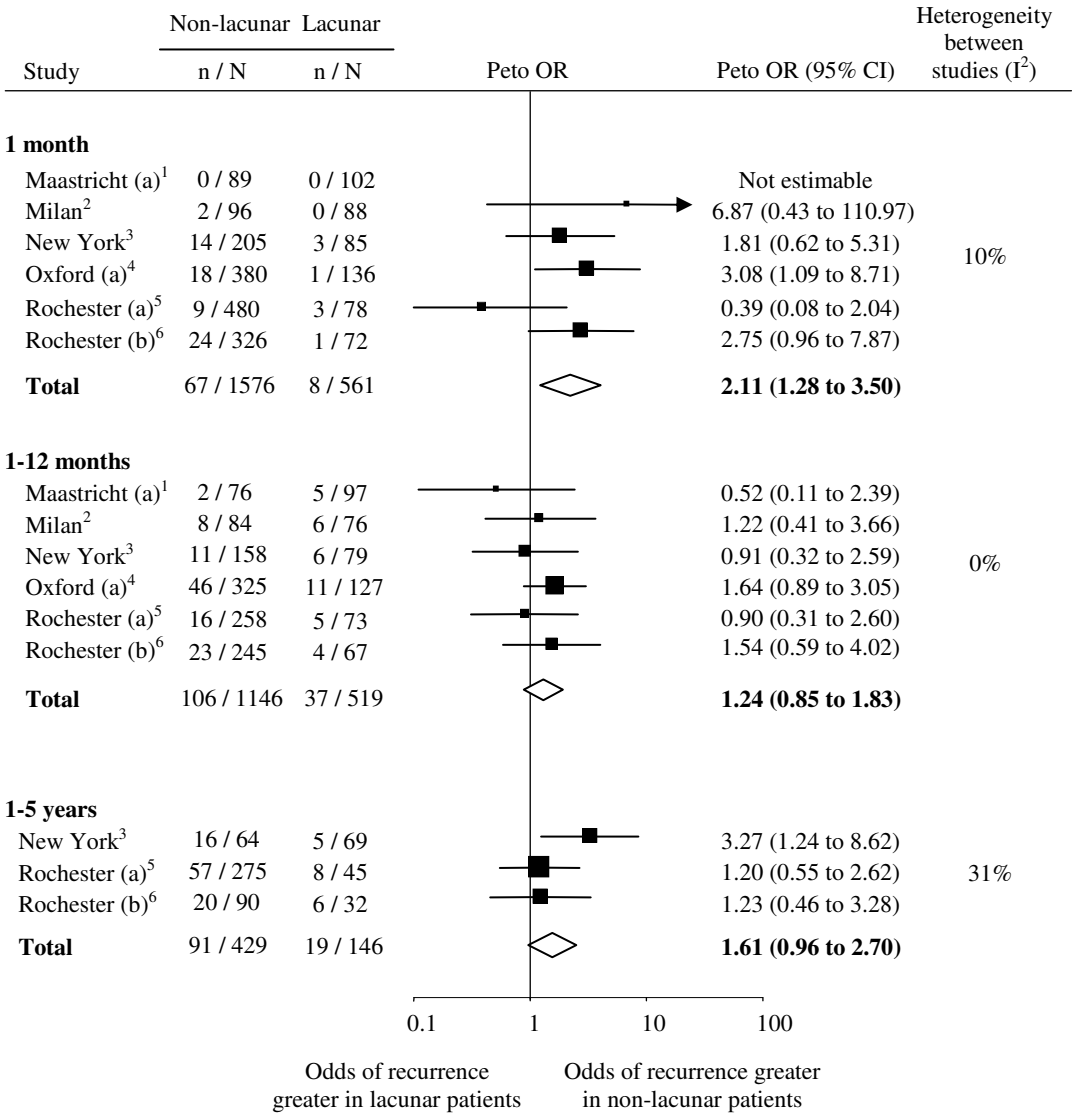
The odds of recurrent stroke in the first month were just over two times greater in non-lacunar compared with lacunar ischaemic stroke patients (OR 2.11, 95% CI 1.28 to 3.50; Figure 4.5), with only mild heterogeneity between studies. Thereafter, the difference in risk attenuated, with no statistically significant difference in the risk of recurrent stroke at 1-12 months (OR 1.24, 95% CI 0.85 to 1.83) or at 1-5 years (OR 1.61, 95% CI 0.96 to 2.70), although, as for mortality, the 1-5 year data are less reliable and available in fewer studies. Where provided, the mean age for lacunar and non-lacunar patients was the same in studies included in the analyses (weighted mean 73 years).

Figure 4.4 Recurrence stroke risks, with 95% CIs at (a) 1-month, (b) 1-12 months and (c) 1-5 years for lacunar and non-lacunar patients



*For references to studies, see Table 4.1 (study references included in footnotes to table)

Figure 4.5 Odds ratios of recurrence at 1 month, 1-12 months and 1-5 years, comparing non-lacunar with lacunar ischaemic stroke



N = total number of patients; n = number of patients with a recurrent stroke. OR = odds ratio; CI = confidence interval.
Squares represent the individual study-specific odds ratio estimates (with size of square reflecting weighting) with the vertical lines representing the 95% CI. Open diamonds represent the overall pooled ORs.

[1]Boiten & Lodder 1991;[2]Landi et al. 1992; [3]Sacco et al. 1994; [4]Bamford et al. 1991; [5]Sacco et al. 1991; [6]Petty et al. 2000

I was unable to include data from 7 relevant studies that reported on recurrent stroke risk. These studies usually reported on the recurrence risk for the entire period for which patients were followed up, and did not generally distinguish between recurrence risk during the early and later time periods. It is therefore difficult to ascertain to what extent the results of these studies agree with those from my meta-analyses. However, after assessing the results of these studies, I found that they do not, on the whole, disagree with those from the included studies (Table 4.1). In two studies where patients were followed for at least 1 year, the authors found no difference in recurrent stroke risk between ischaemic stroke subtypes (Kolominsky-Rabas *et al*. 2001; Soda *et a*l. 2004). In one study, the authors reported a lower risk of recurrence among lacunar compared with cardioembolic patients at one-year, but no difference thereafter. However, it was difficult to determine from the report whether this lack of difference was statistically signficant or not, and whether there was any difference in risk of recurrence between patients with lacunar compared with other types of non-lacunar stroke (Yokota *et al*. 2004).

Where data were reported on recurrent risk in the short term (generally given for between 1 and 6 months), the findings were in keeping with our results, with two studies reporting a lower recurrence risk among patients with lacunar ischaemic stroke at 1 month (Moroney *et al*. 1998; Hier *et al*. 1991) (Table 4.1).

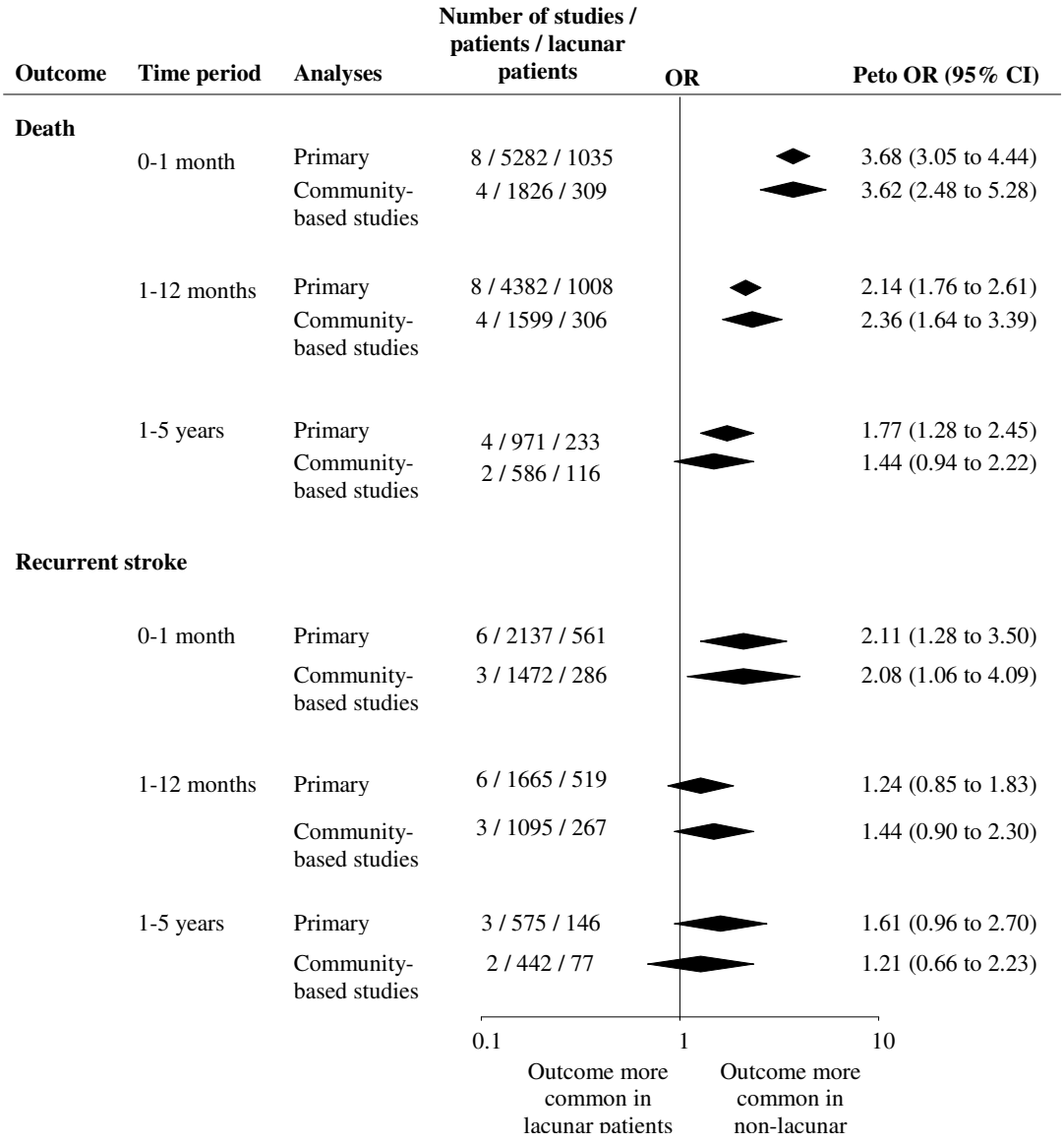
4.4.5 Sensitivity analysis for death and recurrent stroke

I found very similar results to the primary analysis when I repeated the analyses for death and recurrent stroke including only community-based studies (Anderson *et al*. 1994; Bamford *et al*. 1991; Petty *et al*. 2000; Sacco *et al*. 1991). The odds of death at one month were over three and a half times greater in non-lacunar than lacunar

patients, and at 1-12 months, just over two times greater in non-lacunar patients. Two of these studies also provided data for the longer term (Petty *et al*. 2000; Sacco *et al*. 1991) which suggested a trend towards an increased risk of death among non-lacunar patients at 1-5 years, but which was not, however, statistically significant (Figure 4.6)

Three of the community-based studies also reported on recurrent stroke risk at one month and 1-12 months (Bamford *et al*. 1991; Petty *et al*. 2000; Sacco *et al*. 1991), two of which also reported data at 5 years (Petty *et al*. 2000; Sacco *et al*. 1991). Similar to the results of the primary analysis, the odds of recurrence at one month was two times greater among non-lacunar than lacunar patients, but there was no difference in recurrence risk at 1-12 months or 1-5 years (Figure 4.6).

Figure 4.6 Sensitivity analyses for risks of death and recurrent stroke (non-lacunar versus lacunar) including data from only community-based studies or hospital-based studies recruiting from both inpatients and outpatients



Diamonds represent pooled summary odds ratios, with the width of the diamond representing the 95% confidence interval
OR = odds ratio; CI = confidence interval

4.4.6 Recurrent stroke subtype patterns

Four studies (2674 ischaemic strokes, 966 of which were lacunar ischaemic strokes) reported on the pattern of recurrent stroke subtypes following both lacunar and non-lacunar ischaemic stroke patients at baseline (De Jong *et al*. 2004; Hata *et al*. 2005; Hillen *et al*. 2003; Nadeau *et al*. 1993) (Table 4.2). Three studies used a clinical and imaging-based classification method to categorise ischaemic stroke subtypes, and one study used the NINDS classification, which includes some risk factors (but not diabetes or hypertension) in the definitions of ischaemic stroke subtypes. All four studies used a slightly different definition of recurrent stroke (Table 4.4). The main difference was the minimum necessary time interval between index event and recurrent stroke, which was given as 3 days in one study, 21 days in another and unspecified in two studies.

Table 4.4 Details of ischaemic stroke subtype classification method and definition of recurrent stroke in studies of recurrent stroke subtype patterns

Study	Ischaemic stroke subtype classification	Definition of recurrent stroke
Hisayama[1]	Risk factor-based (NINDS)	Standard stroke definition, with added criteria that oedema, haemorrhagic transformation, intercurrent illness or iatrogenesis were excluded as potential causes of any new neurological worsening. Period of neurological stability not specified
London[2]	Risk factor-free (clinical syndrome and brain imaging-based)	Standard stroke definition, with added criterion that oedema, haemorrhagic transformation, intercurrent illness or iatrogenesis were excluded as potential causes of any new neurological worsening, and recurrences within 21 days of the index stroke had to occur in a different part of the brain from the index event
Maastricht (b)[3]	Risk factor-free (clinical syndrome and brain imaging-based)	Standard stroke definition, with added criteria that side effects of drug therapy or intercurrent illness were excluded as potiential explanations for any neurological worsening, and recurrences defined as occurring at least 72 hours after the index stroke
USA[4]	Risk factor-free (clinical syndrome and brain imaging-based)	Standard stroke definition, following a period of neurological stability, the length of which was not specified

[1]Hata *et al*. 2005; [2]Hillen *et al*. 2003; [3]De Jong *et al*. 2004; [4]Nadeau *et al*. 1993

In all four studies the authors reported on the proportion of patients who underwent brain imaging following the baseline stroke, which ranged from 37% to 100% (Table 4.5). CT or MRI was used in two studies (Hata *et al*. 2005; Hillen *et al*. 2003), and CT alone was used in the other two studies (De Jong *et a*l. 2004; Nadeau *et al*. 1993). One study did not report on whether patients with recurrent stroke underwent brain imaging (Nadeau *et al*. 1993). One study reported use of CT in 61% of recurrent stroke patients (De Jong *et al*. 2004) and in the other two studies CT or MRI was used in 40% (Hata *et al*. 2005) and 65% (Hillen *et al*. 2003) of recurrent stroke patients, although neither of these studies specified to what extent MR brain imaging was used, or whether DW MRI was performed (Table 4.5). One of these three studies did carry out detailed autopsy in patients who died during follow-up, so that 94% of recurrent stroke patients had either an autopsy or brain imaging (Hata *et al*. 2005).

In these four studies there were a total of 147 recurrences following lacunar ischaemic stroke at baseline, and 238 recurrences following non-lacunar ischaemic stroke at baseline. The proportion of recurrences that were lacunar again following a lacunar ischaemic stroke at baseline ranged from 32% to 55%, and the proportion of recurrences that were non-lacunar again following a non-lacunar stroke at baseline ranged from 56% to 88% (Table 4.5).

Table 4.5 Brain imaging and characteristics of recurrences among patients with a recurrent stroke following either lacunar or non-lacunar ischaemic stroke at baseline

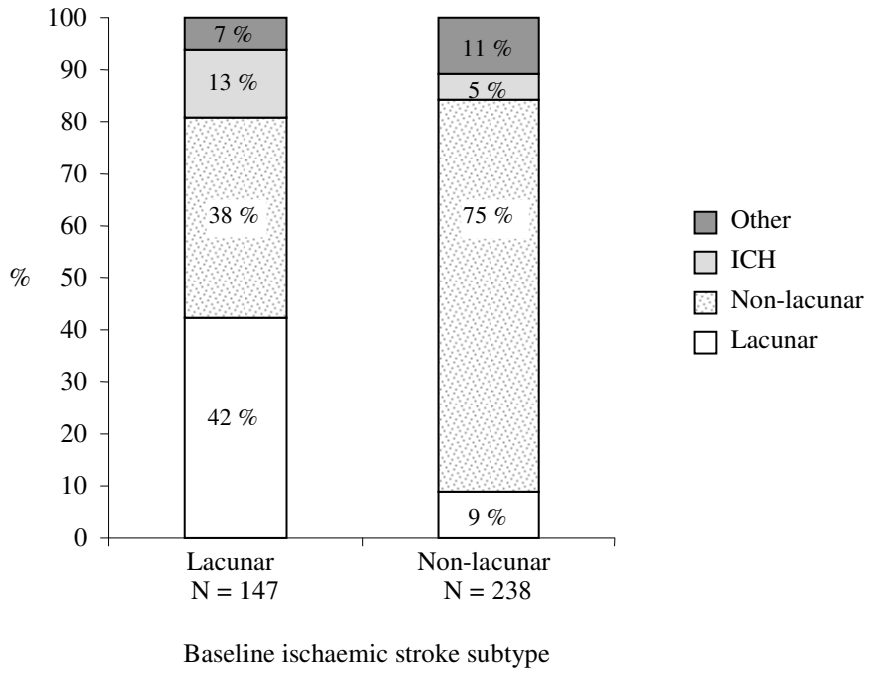
	Brain imaging among recurrences		Type of recurrences following lacunar ischaemic stroke at baseline					Type of recurrences following non-lacunar ischaemic stroke at baseline				
Study	**Type of brain imaging**	**% with brain imaging**	**All (N)**	**Lacunar n (%)**	**Non-lacunar n (%)**	**ICH n (%)**	**Other n (%)**	**All (N)**	**Lacunar n (%)**	**Non-lacunar n (%)**	**ICH n (%)**	**Other n (%)**
Hisayama[1]	CT or MR	40	51	18 (35)	22 (43)	9 (18)	2 (4)	34	1 (3)	30 (88)	1 (3)	2 (6)
London[2]	CT or MR	65	37	12 (32)	16 (43)	4 (11)	5 (14)	66	15 (23)	37 (56)	4 (6)	10 (15)
Maastricht (b)[3]	CT	61	49	27 (55)	14 (29)	6 (12)	2 (4)	89	4 (4)	71 (80)	6 (7)	8 (9)
USA[4]	NR	NR	10	5 (50)	4 (40)	NR	1 (10)	49	2 (4)	40 (82)	NR	7 (14)
All studies	-	-	147	62	56	19	10	238	22	178	11	27

CT = computed tomography; MRI = magnetic resonance; NR = not reported; ICH = intracerebral haemorrhage; Other = undetermined stroke subtypes.
N = total number of recurrences in each study; n = number of each type of recurrence in each study

[1]Hata *et al*. 2005; [2]Hillen *et al*. 2003; [3]De Jong *et al*. 2004; [4]Nadeau *et al*. 1993

When I pooled data from these studies, I found that following lacunar ischaemic stroke nearly half the recurrences were lacunar again, and just over one third were non-lacunar (Figure 4.7). Following non-lacunar ischaemic stroke at baseline, three quarters of the recurrences were non-lacunar again, and just 9% were lacunar. There appeared to be a greater proportion of intracerebral haemorrhages among the recurrent strokes following lacunar ischaemic stroke as compared with non-lacunar ischaemic stroke, but this was based on quite small numbers of haemorrhages (Figure 4.7 and Table 4.5).

Figure 4.7 Type of recurrent stroke following each of lacunar and non-lacunar ischaemic stroke at baseline



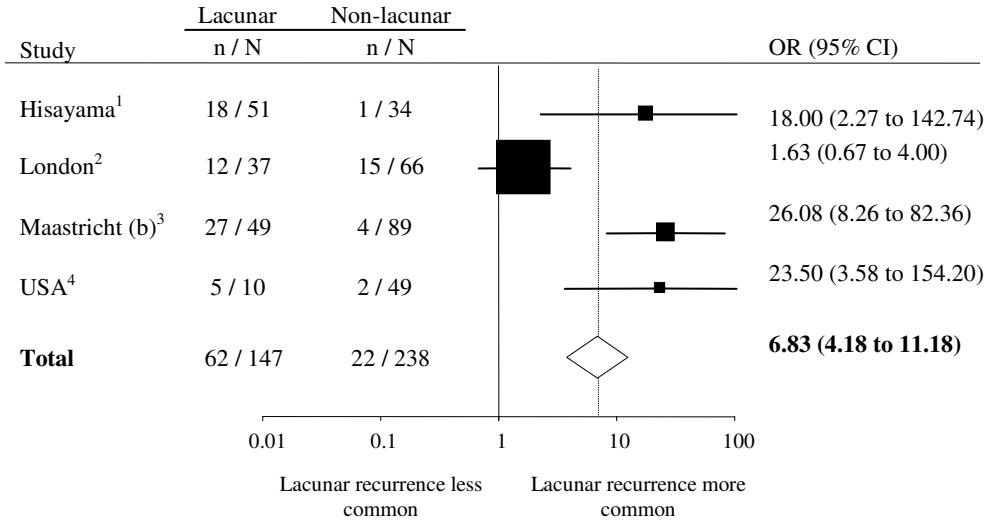
Other = strokes due to unusual causes and uncertain ischaemic subtypes; ICH = intracerebral haemorrhage

In a second analysis I pooled these data together to determine the odds of having a lacunar recurrence following lacunar versus non-lacunar stroke at baseline and a non-

lacunar recurrence following lacunar versus non-lacunar stroke at baseline. The odds of a further lacunar recurrence among lacunar patients was over six times the odds of a lacunar recurrence among non-lacunar patients (OR 6.83, 95% CI 4.18 to 11.18; Figure 4.8). However, there was substantial heterogeneity between these studies which could be explained by the results of one study in which the effect estimate was much less extreme (Hillen *et al*. 2003). This was largely due to the noticeably higher proportion of recurrences that were lacunar following non-lacunar ischaemic stroke at baseline in this study (23%) compared with in the other three studies (3% to 4%). The odds of a non-lacunar recurrence was 80% lower following a lacunar compared with a non-lacunar stroke at baseline (OR 0.20, 95% CI 0.13 to 0.32; Figure 4.8), with substantial heterogeneity between studies again explained by the results of one study (Hillen *et al*. 2003).

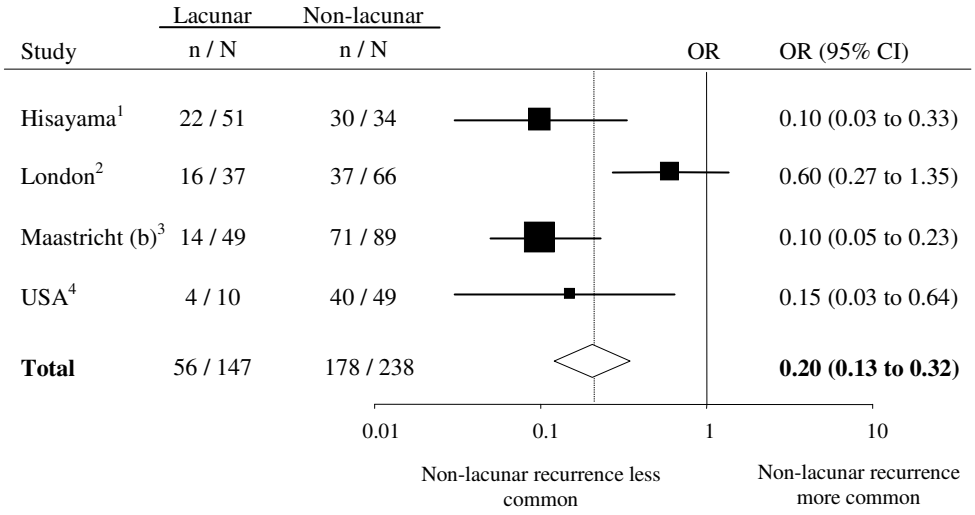
Figure 4.8 Odds ratios for (a) lacunar recurrence and (b) non-lacunar recurrence following lacunar versus non-lacunar ischaemic stroke at baseline

(a)



Heterogeneity between studies: $I^2 = 83\%$

(b)



Heterogeneity between studies: $I^2 = 73\%$

In (a), n = number of patients with a lacunar recurrence and N = total number of either lacunar or non-lacunar patients who had a recurrence.
In (b), n = number of patients with a non-lacunar recurrence and N = total number of either lacunar or non-lacunar patients who had a recurrence.
Open diamond represents the pooled summary estimate
OR = odds ratio; CI = confidence interval.

[1]Hata *et al*. 2005; [2]Hillen *et al*. 2003; [3]De Jong *et al*. 2004; [4]Nadeau *et al*. 1993

If recurrent ischaemic stroke subtypes do not breed true, and the type of recurrent stroke is not related to the index subtype, we would expect the distribution of subtypes to be similar to the distribution of ischaemic strokes generally observed in studies of first-ever strokes. Thus we would expect about 24% of recurrences to be lacunar ischaemic strokes, and about 57% to be non-lacunar ischaemic strokes based on the frequency of these subtypes in two community-based studies (Bamford *et al*. 1991; Hillen *et al*. 2003). In my third and final analysis of recurrent stroke subtype patterns I compared the observed pattern of recurrences to the expected pattern. In the four studies included in my meta-analysis, the proportion of recurrences that were lacunar again following a lacunar ischaemic stroke at baseline was 71% greater than expected (observed number of lacunar recurrences = 62; expected number of lacunar recurrences [0.24*147] = 36; RR observed to expected 1.71, 95% CI 1.31 to 2.19). The proportion of recurrences that were non-lacunar following a non-lacunar index event was 30% greater than expected (observed number of recurrences that were non-lacunar = 178; expected number of non-lacunar recurrences [0.57*238] = 135; RR observed to expected 1.31, 95% CI 1.13 to 1.52).

4.4.7 Myocardial infarction

My search identified just one study that prospectively followed both lacunar and non-lacunar patients for MI incidence, reporting just 6 MIs among 191 patients in total, during a median follow-up of 28 months (Landi *et al*. 1992). There were an additional five small studies reporting on MI among lacunar patients (24 MIs among 533 patients), but these studies did not include a non-lacunar group of patients, and often recorded fatal MI events only (Gandolfo *et al*. 1986; Kazui *et al*. 2001; Salgado *et al*. 1996; Samuelsson *et al*. 1996; Yamamoto *et al*. 2002).

4.5 Discussion

In my systematic review and meta-analyses of existing published studies I found that the risk of death at one month was greater among patients with non-lacunar than lacunar ischaemic stroke. However, when the early period (first month) was excluded, the difference in risk thereafter (between 1-12 months) attenuated. This may suggest that much of the difference in one year death rates between lacunar and non-lacunar patients is accounted for by the early effects of infarct size, and early risk of recurrent stroke. However, persistent differences in risk of death remained at 1-12 months and also in the longer term at 1-5 years (although the latter result is less reliable). This may reflect a true increased risk of death among non-lacunar patients in the early and in the late post-stroke period, or it may be the effect of confounding factors. Stroke severity, for example has been shown to be a strong independent predictor of long-term survival (Eriksson *et al*. 2008; Slot *et al*. 2008). Thus the differences in survival among patients with lacunar versus non-lacunar stroke may well reflect differences in stroke severity.

After one month, I found no statistically significant difference in the risk of recurrent stroke between patients with lacunar and non-lacunar ischaemic stroke. The higher early recurrence risk among patients with non-lacunar ischaemic stroke patients confirms previous work on early recurrence risk among ischaemic stroke subtypes (Lovett *et al*. 2004). It also suggests that there is a greater prevalence of active sources of thrombotic emboli among patients with non-lacunar ischaemic stroke, which supports the results of my systematic review which showed that both a cardioembolic source and severe carotid stenosis are much more common in patients with non-lacunar compared with lacunar ischaemic stroke.

Interestingly, the difference in survival and recurrence in the long-term (at 1-5 years) beween patients with lacunar versus non-lacunar ischaemic stroke attenuated in the more recent studies, perhaps reflecting improvements in post-stroke care and secondary prevention (which may have had more impact on the outcome of more severe strokes).

4.5.1 Limitations of death and recurrent stroke analyses

A number of methodological limitations affect my death and recurrent stroke analyses. First, relevant studies identified in my search reported on risks of outcome events at varying time points, making it impossible to include data in pooled analyses from every potentially relevant study identified. Second, the total number of outcome events, particularly recurrent strokes, was relatively small, which reduced the precision of the effect estimates. Third, I was only able to perform univariate analyses, and thus was unable to control for potential confounding factors such as age, sex and co-morbidity. Other potential confounders include interventions such as carotid endarterectomy and anticoagulation, which are usually tailored to stroke subtype. Both interventions are generally used more often following non-lacunar than lacunar ischaemic stroke. Furthermore, there may be differential effects on recurrent stroke subtypes, since available evidence from randomised trials and observational studies of oral anticoagulation suggests that this treatment is more effective in the prevention of cardioembolic than other types of ischaemic stroke (Evans *et al*. 2000; Hart *et al*. 2000). However, available data do not suggest a definite difference in the effectiveness of carotid endarterectomy between symptomatic patients presenting with non-lacunar versus lacunar ischaemic stroke (Inzitari *et al*. 2000). Neither is there clear evidence to suggest that carotid

endarterectomy prevents a greater proportion of subsequent non-lacunar than lacunar ischaemic strokes (Barnett *et al*. 2000). Fourth, the clinical distinction between lacunar and non-lacunar ischaemic stroke is not perfect, as discussed in the previous chapter. Around 10-20% of patients with a clinical lacunar syndrome actually have a recent relevant cortical infarct which explains the clinical symptoms on brain imaging, and vice-versa (Mead *et al*. 1999a). When there is no lesion present on imaging (and stroke subtype is therefore determined by clinical syndrome), around one fifth of lacunar and small cortical ischaemic strokes may therefore be misclassified. This proportion could be reduced in future studies by the more frequent use of advanced MR brain imaging, especially when the CT scan does not show a relevant infarct. I did not have the individual patient data from the studies included in my analyses, and so could not estimate the degree of misclassification in these studies. However, if the degree of misclassification was indeed similar between the lacunar and non-lacunar comparison groups, then the effect of this misclassification would be to reduce the apparent size of any real epidemiological differences between lacunar and non-lacunar ischaemic stroke.

Finally, the data on very early risk of stroke should be interpreted with caution because of varying stroke recurrence definitions. In some studies, the risk of recurrence within the first month may have been underestimated if early recurrences involving the same arterial territory, or resulting in similar symptoms to the index event, were not always considered as recurrent strokes. There may also have been some overlap between the definition of recurrent stroke and stroke-in-progression. Stroke-in-progression has been defined recently by one group, the European Stroke Database collaboration, as "neurological progression occurring within the first three

days" (Birschel *et al*. 2004). Stroke-in-progression is thought to be particularly common in lacunar stroke (Nakamura *et al*. 1999), therefore very early recurrences among lacunar patients may not be counted as such and may instead be considered part of the evolution of the initial stroke. It has been recommended by some that neurological worsening occurring at any time after the index event, following a period of stability of ≥ 24 hours should be considered a potential recurrent stroke. Otherwise the very early recurrence risk will be underestimated (Coull & Rothwell 2004).

4.5.2 Evidence for a distinct lacunar arteriopathy?

Notwithstanding the methodological limitations outlined above, my findings on the longer term risks of recurrent stroke (which are less likely to be subject to stroke recurrence definition bias) do not provide support for fundamentally different arterial pathologies in lacunar and non-lacunar ischaemic stroke. For, although the risk of death appears to be lower in lacunar patients, which may reflect a distinct lacunar pathology - perhaps due to patients with lacunar ischaemic stroke being less likely to have systemic atherosclerosis and thus having a reduced risk of MI - it may also be due to confounding by factors such as age, sex, infarct size and stroke severity. Comparison of risk of death is therefore potentially less informative in determining whether there is a distinct lacunar arteriopathy.

My analyses on recurrent stroke subtypes do provide some evidence that recurrent stroke subtypes "breed true", lending some support to the hypothesis of a different arterial pathology underlying lacunar ischaemic stroke. However, as mentioned above, there will have been some misclassification of ischaemic stroke subtypes, both at baseline and following recurrent events. Recurrent stroke subtypes in

particular may not have been very accurately classified since brain imaging rates among recurrences were generally quite low and no study reported use of DW MRI, which is particularly useful in differentiating between old and recent infarcts and in establishing the infarct subtype. In patients with residual deficits from their first stroke, suspected recurrences in the same arterial territory as the index event can be particularly difficult to diagnose and classify without the help of advanced MR imaging. It is difficult to predict the effect of such misclassification on the results, but it is possible that, in the face of uncertainty, the stroke subtype assigned is more likely to be the same as that of the first stroke. In addition, in my analyses of recurrent stroke subtypes I could not assess or control for the differential use of secondary preventive interventions such as anticoagulation and carotid endarterectomy in different subtypes of ischaemic stroke, since these data were not reported. The definition of recurrent stroke may also have impacted on the pattern of recurrent stroke subtypes obtained in some studies. In one study reporting on recurrent stroke subtypes there was a trend towards evidence of recurrent subtypes breeding true, but the results were noticeably less extreme compared with those of the other three studies (Hillen *et al*. 2003). The definition of recurrent stroke used in this study did differ markedly from that used in the other studies. The minimum necessary time period between index and recurrent stroke, was longer than in other studies, with recurrences occurring before 21 days in the same area of the brain as the index stroke excluded. The use of this definition may therefore have underestimated the extent to which stroke subtypes breed true in this study, since early recurrences occurring in the same territory would not have been included. The method of classifying ischaemic stroke subtypes may impact on patterns of recurrent

stroke subtypes, especially if risk factors are included in the definitions of ischaemic stroke subtypes, since risk factors are unlikely to have changed between the onset of first and recurrent stroke. Thus, studies using such classification methods may overestimate the degree to which stroke subtypes breed true. However, classification bias is unlikely to have substantially affected the patterns of recurrent stroke subtypes reported in these studies, since three of the four studies used risk factor-independent clinical and brain imaging-based classification methods.

There were very few available data on the risk of MI following different ischaemic stroke subtypes, making it impossible to draw any conclusions about the risk of MI across different ischaemic stroke subtypes.

4.5.3 Conclusion

In conclusion, risk of death in the short and long-term appears to be lower in patients with lacunar compared with non-lacunar ischaemic stroke, which may reflect differences in underlying arterial pathologies or simply differences in age, sex, infarct size and stroke severity. While differences between lacunar and non-lacunar ischaemic stroke patients in the early risks of recurrent stroke suggest different predominant mechanisms in terms of the arterial occlusive source, available data on the longer term risks of recurrent stroke do not provide convincing support for fundamentally different arterial pathologies. Recurrent stroke subtype patterns provide some evidence for different arterial pathologies, but existing studies have methodological limitations. Data on long term risks of MI after lacunar versus non-lacunar ischaemic stroke are too sparse to draw any conclusions.

B. The Edinburgh Stroke Study: design and methodology

Chapter 5. Edinburgh Stroke Study: rationale, aims, design and methodology

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5.1 Aim

In this chapter I will describe the rationale, aims, design and methodology of the Edinburgh Stroke Study, and will refer to these details in the succeeding section where I present results of analyses that include data from the Edinburgh Stroke Study.

5.2 Rationale of the Edinburgh Stroke Study

As I described in my introductory chapters, a better understanding of the aetiology of the ischaemic stroke subtypes should ultimately lead to improvement in the treatment of stroke. I have also described the lack of knowledge surrounding the arteriopathy underlying most lacunar ischaemic stroke in particular, and identified the methodological limitations of existing epidemiological observational studies through systematic review and meta-analysis of published studies. The Edinburgh Stroke Study (ESS) was set up to address some of the unanswered questions and areas of controversy relating to the causes and consequences of stroke, with a particular focus on lacunar ischaemic stroke.

5.3 Aims

In the ESS we recruited and followed up a large cohort of stroke patients, the three principal aims of the study being as follows:

1. to compare the risk factor profiles of patients with different ischaemic stroke subtypes, and in particular to determine whether hypertension and diabetes really are more common in lacunar patients;
2. to determine whether the risks of vascular events (recurrent stroke and myocardial infarction) differ between ischaemic stroke subtypes, and to compare the pattern of recurrent strokes following different stroke subtypes;
3. to obtain blood samples from patients for future analyses of genotypes and other biomarkers.

5.4 Ethical approval

We sought and obtained ethical approval for the study from the Lothian Research Ethics Committee and approval for the study to occur in an NHS facility from the Lothian NHS Research & Development department.

5.5 Patient eligibility and consent

We prospectively recruited consenting patients with stroke, transient cerebral or monocular ischaemic attack (TIA) or retinal artery occlusion, admitted to, or seen in outpatient clinics at, the Western General Hospital, Edinburgh between April 2002 and May 2005. Patients had to have been clinically assessed at the Western General Hospital within 6 months of the date of their cerebrovascular event. Stroke was defined as the sudden onset of clinical signs of focal disturbance of cerebral function lasting more than 24 hours with no apparent cause other than that of vascular origin (Aho *et al*. 1980), and we recruited patients with ischaemic stroke or intracerebral haemorrhage but not those with subarachnoid haemorrhage.

A clinical stroke specialist (consultant, registrar or clinical research fellow) assessed patients as soon after their stroke, TIA or retinal artery occlusion as possible.

Informed consent was required and sought from all patients. Eligible patients (or their relatives) received a simple concise information leaflet explaining the details of the study (Appendix 5) and a short consent form, with time to read and consider these before the consultation with the doctor. Patients who desired further time to consider whether to give their consent were given the option of returning the consent form to the study team by post. The consent form consisted of four components (Appendix 6). Patients could consent to any or all of the following:

- use of their collected data for research purposes;
- contact with their General Practitioner (GP) and access to their medical record;
- further follow-up contact;
- and collection of a blood sample to be stored for future analyses of genotypes and other biomarkers.

A relative could provide assent when patients were unable to provide consent for themselves. Where the patient was able to understand and to give verbal but not written consent, their clinician could provide signed witnessed consent. Waiver of consent (for use where the patient was cognitively impaired – sometimes as a result of the stroke – and where there were no relatives or other substitute decision makers available to provide proxy consent) was originally approved for use by the Ethics Committee. However, the introduction of the Adults with Incapacity (Scotland) Act 2002 shortly after the start of patient recruitment meant that, for the remainder of the study, waiver of consent was not allowed to be used for living incapacitated patients with no available proxy. We were however still able to include patients who died during admission to hospital, and were no longer covered by the UK Data Protection Act 1998.

5.6 Baseline data collection

We obtained data prospectively using a standardised structured questionnaire, completed by the clinician at the time of assessment, using information from the patients and/or their relatives; the patient's GP; and patient's medical records. The questionnaire used to collect data from inpatients is included in Appendix 7. We used a slightly different form to collect data from patients assessed in outpatient clinics, in order to collect additional data required by the parallel running clinical stroke audit (Appendix 8). Both forms were developed from existing data collection forms used in the ongoing clinical stroke audit, and were designed specifically to be used by clinicians who could complete them during the process of normal clinical assessment of patients. The key data items collected are summarised in Table 5.1. The study team's lead clinician (CLMS) reviewed the medical records of all patients reported to have an unusual cause of or risk factor for stroke to determine whether the potential unusual cause was definitely or probably the cause of the stroke, allowing us to classify and code these patients appropriately in the dataset. Rare, unusual specific causes of stroke included those where there was clear evidence of a rare cause of stroke that could not be assigned to one or a combination of large artery atherothrombotic or atherothromboembolic disease, cardiac thrombotic embolism, small artery (lacunar) disease. These rare causes included: bacterial endocarditis; atrial myxoma; giant cell arteritis and other vasculitides; arterial dissection; radiotherapy induced large or small vessel disease; monogenic disorders such as CADASIL; and intracranial venous sinus thrombosis.

Table 5.1 List and description of key data items collected in the ESS

Data item	Details / definitions
Consent for ESS	Type of consent (patient, relative etc) and components of study consented to)
Final diagnosis	Stroke / TIA
Clinical Assessment	
NIHSS score	At time of clinical assessment
Date of onset of symptoms	-
Antiplatelet treatment at onset	On aspirin or on other antiplatelet treatment
Anticoagulant treatment at onset	On warfarin
Side of brain lesion	Right / left / cerebellar or brainstem / bilateral / uncertain
Blood pressure at time of assessment	-
Risk factors	
Previous stroke	Previous clinically apparent stroke
Previous TIA	Transient cerebral or monocular symptoms lasting ≤24 hours
IHD	Previous MI, angina, CABG, coronary angioplasty or stent
Hypertension	History of treated hypertension
Diabetes mellitus	History of type I or type II diabetes mellitus
Cardiac failure	Clinical signs of heart failure or taking at least two drugs for its treatment
Atrial fibrillation	History of paroxysmal or persistent atrial fibrillation
Social and family history	
Cigarette smoking	Never / current / ex > 12 months / ex ≤ 12 months
Alcohol intake	Units per week
1st degree relative with stroke	Mother / father / sibling / children as reported by patient or relative
1st degree relative with IHD / PAD	Mother / father / sibling / children as reported by patient or relative
Clinical classification of stroke / TIA Syndrome	OCSP classification (TACS, PACS, LACS, POCS, uncertain)
Details of other risk factors or unusual causes	Arterial dissection; hereditary conditions such as CADASIL; patent foramen ovale etc

Table 5.1 continued

Data item	Details / definitions
Clinical investigations	
Blood tests	Full blood count (haemoglobin etc) and biochemistry (creatinine etc)
Cardiac investigation (ECG / ECHO)	Evidence of AF on ECG and LVH on ECG and ECHO
Carotid imaging results	Type of carotid imaging performed; degree of internal carotid artery stenosis (%); post-stenotic collapse; plaque instability
Brain imaging	Type of brain scan performed; evidence of new relevant lesion
Final OCSP classification subtype	OCSP syndrome modified by site and size of relevant lesion on brain imaging

ESS = Edinburgh Stroke Study; NIHSS = National Institute for Health Stroke Scale; TIA = transient ischaemic attack; IHD = ischaemic heart disease; PAD = peripheral arterial disease; MI = myocardial infarction; CABG = coronary artery bypass graft; OCSP = Oxfordshire Community Stroke Project; TACS = total anterior circulation stroke; PACS = partial anterior circulation stroke; LACS = lacunar stroke; POCS = posterior circulation stroke; CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; ECG = electrocardiogram; AF = atrial fibrillation; ECHO = echocardiogram

5.7 Ischaemic stroke subtype classification

The clinician assessing the patient first assigned a clinical stroke syndrome according to the patients' symptoms and signs at maximal deficit, using the OCSP classification (Bamford *et al*. 1991). This classifies patients according to whether they had a total anterior circulation stroke (TACS), partial anterior circulation stroke (PACS), lacunar stroke (LACS), posterior circulation stroke (POCS), or an uncertain stroke syndrome. We then assigned a final ischaemic stroke subtype classification based on the clinical syndrome modified where appropriate by the site and size of any visible relevant infarct(s) on brain imaging. We classified a patient as having a lacunar ischaemic stroke (LACI) if they had a clinical lacunar syndrome with either no visible relevant infarct or a visible relevant subcortical infarct (located in the

thalamus, basal ganglia, internal or external capsule, or centrum semiovale) measuring ≤ 20mm on brain imaging, or if they had a cortical syndrome with a relevant subcortical lacunar infarct that accounted for their symptoms. We classified a patient as having either a partial anterior circulation infarction (PACI) or a total anterior circulation infarction (TACI) (depending on the specific cortical symptoms), if they presented with a cortical-involving anterior circulation syndrome with or without an accompanying visible relevant cortical or striatocapsular infarct on brain imaging or if they presented with a clinical lacunar or posterior circulation syndrome but had a cortical-involving or striatocapsular infarct in the anterior circulation territory that was clearly relevant to the presenting stroke. Thus a patient presenting with a partial anterior circulation syndrome, for example, but with a visible relevant lacunar infarct on brain imaging in a location which explained the stroke symptoms, was reclassified as having a lacunar ischaemic stroke. We classified patients as having posterior circulation infarction (POCI) if they presented with a posterior circulation syndrome with or without an accompanying relevant infarct on brain imaging, or with an anterior lacunar or cortical syndrome but a visible relevant infarct in the posterior circulation. We classified patients as having an uncertain syndrome when they presented with an unclassifiable clinical syndrome which also could not be classified from brain imaging findings.

We discussed all inpatients and selected outpatients (those for whom the clinical diagnosis and/or stroke classification required further discussion) at a weekly stroke register meeting attended by expert stroke clinicians, neuroradiologists and stroke research fellows. The assessing clinician presented the clinical details of each patient and we discussed these, and reviewed the brain imaging before agreeing on the final

diagnosis and stroke pathological type and subtype. The stroke specialist consultant responsible for each of the remaining outpatients assigned their final diagnosis and subtype classification after review of all relevant clinical details and brain imaging findings.

5.7.1 Definition of cardioembolic source

We assigned patients as having a potential cardioembolic source of stroke or TIA if they had a problem of cardiac rhythm, structure or function that increased risk of cardiac embolism, including:

- history of persistent or paroxysmal atrial fibrillation or flutter, or if they had atrial fibrillation or flutter on their post-stroke or TIA ECG;
- native cardiac valve disease or cardiac valve replacement causing an increased risk of cardioembolic phenomena;
- patent foramen ovale +/- atrial septal aneurysm with no other vascular risk factors that may have provided an alternative cause for the stroke or TIA
- active endocarditis at the time of their stroke (bacterial endocarditis also considered rare, unusual cause)
- recent myocardial infarction (within last few weeks; although visible cardiac thrombus not necessary)
- dilated cardiomyopathy
- atrial myxoma (also considered rare, unusual cause)

5.8 Method of follow-up

We followed patients up for a minimum of one year and a maximum of four years. Our primary outcomes were death; recurrent stroke; myocardial infarction (MI); and disability as measured by a self-reported Modified Rankin score (van Swieten *et al*.

1998) at 6 months, one year and annually thereafter. The outcomes that were of primary interest for my thesis were death, recurrent stroke and MI.

In the follow-up component of our study we included all recruited patients diagnosed with a stroke from whom we had obtained consent for future contact and who were living in the Edinburgh area (i.e. had a postcode beginning "EH").

We used several overlapping methods of follow-up in an attempt to ensure as complete follow-up as possible for relevant outcomes. Patients received postal questionnaires at 6 months from their stroke onset date, one year and annually thereafter for at least one year and for a maximum of four years (Appendix 9). The postal questionnaire was modified from a previous follow-up questionnaire used in the Lothian Stroke Register, which recruited patients from the same target population during the 1990s (Wardlaw *et al*. 1998). Questionnaires were completed by the patient (or a relative or carer) and returned by post to the study team. In the questionnaire we enquired whether patients had had further vascular events since their stroke (or since we were last in contact with them, whichever was most recent). The brief questionnaire included questions on the following:

- where and how the patient lived now (on their own, with relatives etc);
- whether or not they had had further weakness in their face, arm or leg, or problems with vision or speech (since previous stroke or last contact);
- whether a doctor had told them they had had a stroke (since previous stroke or last contact);
- whether or not they had had chest pains (since previous stroke or last contact);
- whether they had been told they had had a heart attack (since previous stroke or last contact);

- and their activities of daily living (through completion of a self-rated modified Rankin scale) (van Swieten *et al*. 1998).

We sent patients a reminder questionnaire one month after the first questionnaire was sent if the first questionnaire had not been returned within that time. If patients did not return the reminder postal questionnaire for a particular point in their follow-up, we interpreted this as implicit withdrawal from this aspect of the study and did not send any further questionnaires.

We also provided patients with a stroke study contact card (Appendix 10) at time of recruitment, and asked them to contact the team should they have a further suspected stroke or a heart attack. We informed GPs by letter when a patient was recruited into the study, providing them with an ESS alert sticker for their GP notes (Appendix 10), and asking them to contact the study team in the event of a further stroke or death of the patient. We also added ESS alert stickers to the front of the patients' hospital records to ask clinicians to contact us in the event of the patient being admitted to hospital with a further stroke or myocardial infarction. In addition, at the end of follow-up we also contacted by post the GPs of patients who were still alive to enquire about the occurrence of any further vascular events during the entire follow-up period (Appendix 11).

In addition to these "hot-pursuit" methods, at the end of follow-up we also compared our cohort of patients with those included in a concurrent clinical stroke audit that prospectively and retrospectively collected data on patients diagnosed with a stroke either as an inpatient or outpatient at the Western General Hospital and the Royal Infirmary of Edinburgh (Edinburgh's only other large general hospital admitting

patients with stroke), to identify any recurrent stroke events that we may have missed via our other methods.

Finally, we arranged for all patients to be flagged at the General Register Office for Scotland (GRO), who routinely provided information on the date and place of death, whether or not an autopsy was performed, the certifying doctor, and the cause of death.

5.9 Identification and definition of vascular outcomes

5.9.1 Recurrent stroke

We identified recurrent stroke events using the overlapping methods of ascertainment described above.

We defined recurrent stroke using the same criteria as for index stroke, with the added criterion that there had to have been a period of neurological stability of at least 24 hours between the occurrence of index and recurrent stroke. Alternative causes for neurological decline, such as intercurrent illness, haemorrhagic transformation of an infarct or cerebral oedema, also had to be excluded.

A specialist stroke clinician assessed all patients who suffered an early recurrent stroke whilst still in the Western General hospital. Wherever possible, a stroke clinician assessed in the outpatient clinic those patients who we had identified as having a possible or probable further stroke, but who had not been admitted to the Western General Hospital. Where patients were unable to attend a face-to-face clinical assessment, we confirmed suspected recurrent strokes by independent review of all relevant medical records and results of clinical investigations, including brain imaging. Where a patient had a recurrent stroke, we collected data on the clinical features of the stroke; antiplatelet and anticoagulant treatment at time of stroke; the

clinical stroke syndrome; details of any clinical investigations performed, including type of brain imaging and details of visible relevant brain lesions; and final stroke subtype classification. As with the classification of the index strokes, we assigned recurrent stroke syndromes using a combination of clinical and brain imaging findings (where brain imaging was performed). Where the patient was assessed at hospital and in particular where CT brain imaging showed no new relevant lesion, advanced MR imaging, including diffusion-weighted imaging was performed wherever possible.

5.9.2 Myocardial infarction

We identified MI events using the overlapping methods of ascertainment described above. We confirmed MI events through review of all relevant medical records. We recorded the date of MI and, where clinical assessment and investigations had been carried out, whether there were relevant ECG changes, chest pain or raised troponin. If the patient had died and an autopsy had been performed, we reviewed the autopsy report to confirm whether there was pathological evidence of acute MI.

Diagnosis of a definite MI required either:

(1) evidence of two of the following:

- typical symptoms (e.g. chest pain)
- enzymatic changes indicative of MI (generally raised troponin)
- ECG changes suggestive of new ischaemia (new ST-T changes or left bundle branch block)

or

(2) pathological evidence of acute MI at autopsy

We assigned a diagnosis of probable MI when the patient died suddenly and unexpectedly, without evidence of a non-cardiac cause and with no subsequent autopsy examination.

5.10 Death

When we informed GPs of their patient's involvement in the study, we asked them to inform us if the patient died. We also checked survival status prior to contacting any patient directly during follow-up. Every month we received copies of death certificates for patients in our study from the GRO. Initially, we hoped to review hospital medical (and where necessary GP and nursing home) records for all patients who had died, but we had insufficient resources to do so. Therefore, since identification of recurrent strokes and MI was a key priority, we prioritised for notes review all deaths for which stroke or MI appeared anywhere in part one or part two of the death certificate. In addition, we reviewed the reports of all post-mortem examinations. We also reviewed hospital medical records for the vast majority of in-hospital deaths for which medical records were easy to obtain. In total, we reviewed the medical records of over two-thirds of patients who had died (of any cause). Where we reviewed medical records for cause of death, we assigned our own cause of death separate to that detailed on the death certificate.

5.10.1 Assigning cause of death

We assigned each patient who had died a single cause of death, which was the disease that started the chain of events leading to death. We used all the information available to us (death certificate, medical, nursing and GP records, autopsy reports) to make an assessment of this chain of events. We were also guided by the simple rules for assigning cause of death after stroke in clinical research laid out in Halkes *et*

al., Stroke 2006. In this study, 29 neurologists with an interest in stroke completed a questionnaire relating to classification of death after stroke and assigned cause of death to 5 case vignettes. Stroke severity and post-stroke disability, together with length of time between stroke and death, were found to be key factors taken into consideration by neurologists. On the basis of the responses to the questionnaire and case vignettes, the authors developed simple criteria for classifying death after stroke, a method which performed well in an interobservor study, with good agreement obtained.

Taking these suggested criteria into consideration, we considered a death as being due to stroke wherever the factors leading to the patients' death were clearly related to the stroke (e.g. aspiration pneumonia in a patient with pneumonia, deep vein thrombosis leading to pulmonary embolism in a patient with post stroke immobility). We assigned stroke as the single cause of death if death occurred within a month of a stroke, unless there was an undeniable other cause of death (e.g. myocardial infarction, malignancy, car accident). When a patient died more than one month after stroke, and specific information about the chain of events leading to death was unavailable, we assigned stroke as the single cause of death if the patient's best modified Rankin grade after the stroke had been greater than 3 (i.e. patient had quite severe symptoms and required help from other people, but did not need attention day and night, or had major symptoms and required attention day and night) or if other information (e.g. discharge to a nursing home) suggested that they had been left with significant long term disability after their stroke.

We also categorised each single cause of death as vascular or non-vascular, including deaths due to haemorrhage in the vascular category when the haemorrhage had

occurred as a direct result of the vascular disease (e.g. ruptured aortic aneurysm), and in the non-vascular category when the haemorrhage was not due to underlying vascular disease (eg. upper gastrointestinal haemorrhage from peptic ulcer disease).

5.11 Data checks and manipulation

At the end of the study, we ran data checks to identify missing data in key fields, which I then sought to complete as far as possible through review of medical records, with input from a clinician (CLMS) where necessary. Our computer programmer (AH) performed data manipulation and primary coding of variables.

Chapter 6. Assessing the impact of the requirement for explicit consent in the Edinburgh Stroke Study

6.1 Aim

As described in the previous chapter, we were required to obtain informed consent from patients or their relatives before they could be included in our study. I aimed to assess the impact of this requirement for consent in the Edinburgh Stroke Study, by comparison with a contemporaneous clinical stroke audit that targeted the same population but did not require consent.

6.2 Introduction

As described in the previous chapter, ethics committee approval required that we obtain explicit consent from patients (or their relatives) before including them in the ESS. Our aim was to include all stroke and TIA patients seen in outpatient clinics at, or admitted to, the Western General Hospital during the period of recruitment. However the need for consent from patients inevitably meant that not all eligible patients were included in the study. Patients may not have been recruited because they either refused to participate in the study, or because they were missed for inclusion due to the logistical constraints of the consent process itself. Obtaining consent from patients with stroke can be problematic because patients are sometimes unable to consent for themselves, as a result of dysphasia, cognitive impairment, or reduced conscious level due to stroke. Research involving patients unable to consent for themselves is particularly constrained by current legislation and guidance. The Adults with Incapacity (Scotland) Act 2000, introduced early in the recruitment

phase of the ESS, does not allow consent to participate in medical research to be given by an impartial medical representative (i.e. waiver of consent) in these situations. We therefore had to rely on relatives, where available, of incapacitated patients to provide proxy consent.

Since the ESS is a hospital-based study, it is of course subject to referral bias (whereby patients assessed at or admitted to hospital differ systematically from those who are not, in terms of their demographic characteristics, medical history and/or features of the disease under study). This may affect the generalisability of results of some analyses, but it is possible to predict the type of patients likely to be underrepresented in a hospital-based study, and to consider the effect that this may have on the results of specific research questions. However, it is also important to consider the impact that the requirement for consent may have had in our study, by determining, firstly, the proportion of all eligible patients who were actually included in the ESS, and secondly, whether participants differed in their characteristics from non-participants, to assess whether the requirement for explicit consent introduced response bias, or, as it has recently been termed, "consent bias" (Al-Shahi *et al*. 2005).

I assessed the impact of the consent process in the ESS through comparisons with a concurrent clinical stroke audit that targeted the same population but did not require explicit consent. I determined patients' willingness to participate in the various components of the ESS, and compared baseline characteristics of participants versus non-participants.

6.3 Methods

6.3.1 Clinical stroke audit

The ongoing clinical stroke audit collects data on process of care and key clinical variables on all patients with a stroke or TIA admitted to, or seen in outpatient clinics at, the Western General Hospital, with no requirement for explicit patient consent. Administrative and nursing staff in the audit team identify patients using comprehensive, multiple, overlapping, prospective and retrospective methods. Ethical approval for the audit was given by the Multicentre Research Ethics Committee (as part of a Scotland-wide stroke audit).

6.3.2 Numbers of consenters, refusers, and participants

We assessed participation during an 18-month period in the middle of the recruitment phase (October 2002 through March 2004) which we considered to be representative of the overall recruitment period. We did not analyse data from the entire recruitment phase because firstly, we expected recruitment during the first few weeks of the study to be incomplete while we were piloting and refining our recruitment procedures, and secondly, we had not quite reached the end of the recruitment phase when we started analysing these data.

The clinical audit and the ESS used a common data collection form for outpatients, and so the only reason for a patient who was assessed in outpatients to be in the audit and not in the ESS was lack of consent. Data from inpatients were recorded separately for the audit and the ESS, and as a result the reason that an inpatient was included in the audit and not in the ESS was one of the following:

- discrepancy between the final clinical diagnosis assigned by the audit and by the ESS;

- identification by the audit but not by the ESS;
- identification by the audit and by the ESS but non-inclusion due to patient/relative refusal;
- identification by the audit and the ESS but non-inclusion due to lack of consent for other reasons (e.g. patient discharged before consent could be sought or relatives not available to give consent).

To identify the reasons for non-inclusion in the ESS, we gathered information from a variety of data sources, including a pre-inclusion administrative spreadsheet where we had logged all definite and possible stroke or TIA patients admitted to hospital and whether or not they had given consent to be included in the study; original data collection forms; and, where necessary, medical records of patients in order to confirm the diagnosis of patients identified by the audit but not the ESS.

Where the stroke audit and the ESS had disagreed on whether or not a patient had had a probable or definite stroke, we considered the ESS diagnosis to be more accurate. Although we considered the audit to be superior in terms of case ascertainment (because the latter used both prospective and retrospective methods of identification) we considered the ESS to be superior in terms of accuracy of diagnosis since all patients were assessed by a specialist stroke clinician and, as described in chapter 5, were discussed at our stroke register meeting. In contrast, not all patients identified by the audit had been assessed by a specialist stroke clinician and the decision to include them in the audit as a stroke or TIA was based on review of medical records.

We obtained the total number of patients with a stroke or TIA included in the audit during this time (after excluding those patients where the ESS had assigned a non-stroke/TIA diagnosis. Of these, we determined the number who:

- were approached and gave consent for inclusion in the ESS;
- died in hospital before consent could be obtained, and were thus included in the study because their data was no longer covered by the UK Data Protection Act 1998;
- refused consent to any part of the study;
- were not included in the ESS because they were either not identified prospectively by the ESS, or were identified prospectively but not approached for consent for logistical reasons (which includes patients being discharged before being approached for consent or difficulties in obtaining consent from a relative).

Among consenters, we calculated the proportion with consent given directly from the patient (either signed consent or verbal consent (witnessed by the clinician)) or from a relative. Among those from whom we sought consent, we calculated the proportion giving consent to each of the four consent subcategories described in the previous chapter (use of data for research; contact with GP and access to medical records; follow-up; and collection of a blood sample). We defined and enumerated 'participants' as those included in the ESS (that is, those who gave consent and those who died in hospital before consent could be sought), and 'non-participants' as those not included in the ESS (those who refused consent and those from whom consent was not sought and who were discharged from hospital alive).

6.3.3 Characteristics of participants versus non-participants

I assessed differences between participants and non-participants, comparing variables that had been collected by both the audit and the ESS, which included age; sex; event subtype (TIA, eye attack [transient monocular blindness or retinal artery occlusion], or stroke classified according to the Oxfordshire Community Stroke Project classification (Bamford *et al.* 1991) modified by site and size of relevant lesion(s) on brain imaging); socio-economic deprivation, using the Carstairs deprivation index which assigns a deprivation score based on postcode sector (McLoone 2002) and (for inpatients only) admission to stroke unit and length of stay.

6.3.4 Statistical analyses

I performed statistical analyses using STATA version 8.0 (StataCorp 2003).

I analysed data for inpatients and outpatients separately, using the Mantel-Haenszel χ^2 test to compare categorical variables, Student's t-test to compare continuous variables, and the χ^2 test for trend to compare ordered categorical variables among participants versus non-participants. I adjusted for potential confounding using logistic regression. I modelled the data for inpatients and outpatients separately, including age, gender, event type (PACS, LACS, POCS, TACS, uncertain stroke type and TIA or eye attack) and socioeconomic status in both models, and length of hospital stay and admission to stroke unit in the inpatient model only. I determined the statistical significance of the association between each included variable and participation by comparing a model with the variable to one without the variable using the likelihood ratio test (LRT), with a p-value of less than 0.05 denoting statistical significance. I included age and socioeconomic status assuming a linear

association with participation, since inclusion of these as categorical variables did not improve the fit of the models, which I assessed using the LRT.

6.4 Results

6.4.1 Numbers of participants and non-participants

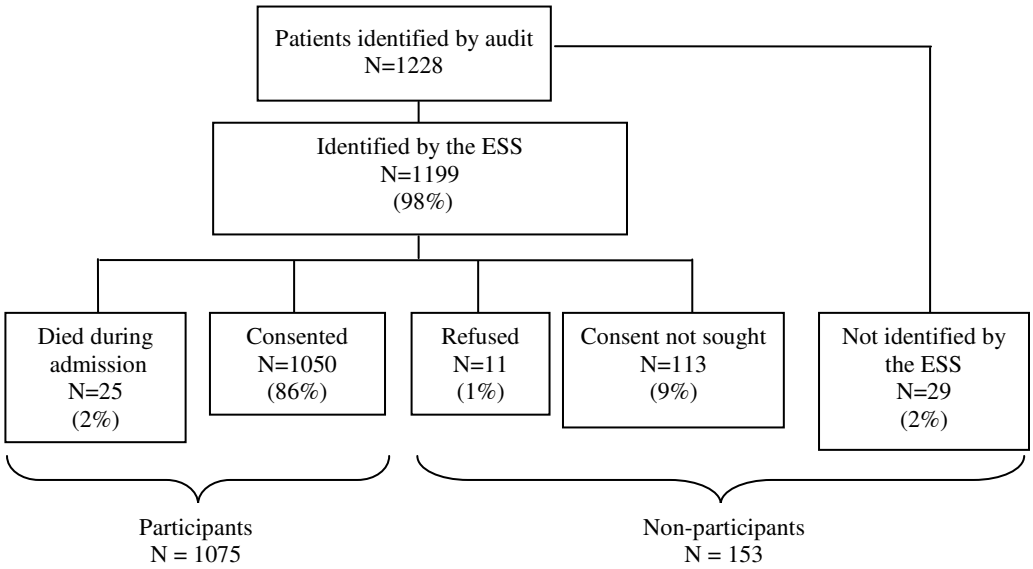
Of 1521 patients included in the audit during the defined time period, 23 patients were diagnosed by the ESS study team as having had a possible stroke or TIA event only. Of the remaining 1228 patients included in the audit and eligible for the ESS, we prospectively identified 1199 (98%), and 1075 of the 1228 (88%) eventually participated in the ESS (Figure 6.1). 1061 patients were approached for consent and we obtained consent from 1050 of these. Twenty-five patients died in hospital before consent could be sought and were also included as participants. Of the 1050 from whom we obtained consent, 94% gave their own consent, with proxy consent from relatives accounting for the remaining 6%.

There were 153 non-participants (12% of the 1228 patients included in the audit). Non-participants comprised 11 of 1228 eligible patients (1%) who refused consent, 29 (2%) who were not identified prospectively by the ESS but were identified by the audit, and 113 (9%) identified by the ESS but from whom consent was not sought (Figure 6.1). Reasons for not seeking consent from identified patients included discharge from hospital before consent could be sought by one of the ESS team, and inability to meet with and obtain signed consent from relatives of patients who were unable to consent for themselves.

The proportion of patients assessed as outpatients in the ESS was greater than the proportion assessed as inpatients. This reflects differences in the catchment area of the outpatient and

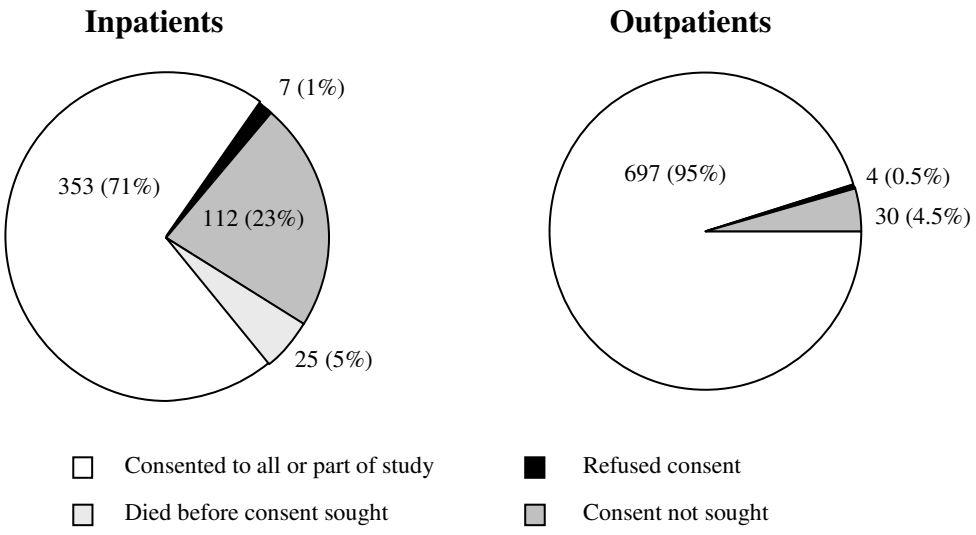
inpatient services of the Western General Hospital, with the catchment area being larger for outpatients.

Figure 6.1 Flow diagram showing participation and non-participation of patients in the Edinburgh Stroke Study



The proportion of patients from whom we sought and obtained consent was higher among outpatients than inpatients, resulting in higher participation rates among outpatients than inpatients (95% vs 76%, p<0.001) (Figure 6.2).

Figure 6.2 Participation in the Edinburgh Stroke Study



Of the 1061 patients approached for consent:

- 1050 (99%) consented to use of their clinical data for research
- 1048 (99%) consented to contact with their family doctor
- 1031 (97%) consented to future direct contact for follow-up purposes
- 1021 (96%) consented to storage of a blood sample

6.4.2 Characteristics of participants versus non-participants

The characteristics of the 1075 participants and 153 non-participants are presented separately for inpatients and outpatients (Tables 6.1 and 6.2). There were no significant differences between participants and non-participants in age or gender among inpatients and outpatients. However, there were differences in other characteristics, particularly for inpatients, among whom participants were significantly more likely than non-participants to be admitted to a stroke unit (77% versus 45%, adjusted p value < 0.001), and to be more affluent (adjusted χ^2 test for trend, p = 0.01). The unadjusted distribution of event type among inpatients also differed significantly between participants and non-participants (p = 0.001): participants had a smaller proportion of TIAs and eye attacks, a greater proportion of mild (lacunar or partial anterior circulation) strokes, and a slightly greater proportion of the most severe (total anterior circulation) strokes (Figure 6.3). However, the relationship became non-significant (p = 0.08) after adjusting for the other variables (Table 6.2).

Table 6.1 Characteristics of participants and non-participants amongst inpatients

Characteristic	All patients (N = 497) n (%)	Participants* (N = 378) n (%)	Non-participants† (N = 119) n (%)	Unadjusted p-value	Adjusted OR participants vs non-participants (95% CI)‡	Adjusted p-value (LRT)¶
Mean age in years (± SD)	74 (± 13)	74 (± 13)	73 (± 14)	0.38	1.00 (0.98 to 1.01)	0.63
Male	226 (45)	176 (47)	50 (42)	0.39	1.00	0.24
Female	271 (55)	202 (53)	69 (58)		0.73 (0.46 to 1.16)	
Event type						
PACS	177 (35.6)	142 (37.6)	35 (29.4)		1.00	
LACS	86 (17.3)	71 (18.8)	15 (12.6)		1.15 (0.57 to 2.32)	
POCS	81 (16.3)	54 (14.3)	27 (22.7)	0.001	0.63 (0.33 to 1.20)	0.08
TACS	90 (18.1)	72 (19.1)	18 (15.1)		0.96 (0.49 to 1.89)	
Uncertain	22 (4.4)	17 (4.5)	5 (4.2)		1.07 (0.35 to 3.28)	
TIA / eye attack	41 (8.3)	22 (5.8)	19 (16)		0.34 (0.15 to 0.74)	
Socio-economic Deprivation score (N = 495)						
1 (most affluent)	46 (9.3)	37 (9.8)	9 (7.6)			
2	102 (20.6)	84 (22.3)	18 (15.1)			
3	93 (18.8)	71 (18.9)	22 (18.5)			
4	118 (23.8)	87 (23.1)	31 (26.1)	0.04#	0.83 (0.72 to 0.96)**	0.01
5	85 (17.2)	62 (16.5)	23 (19.3)			
6	19 (3.8)	13 (3.5)	6 (5.0)			
7 (least affluent)	32 (6.5)	22 (5.9)	10 (8.4)			
Median length of hospital stay (days) [IQR]	17 [5-46]	17 [5-44]	17 [4-57]	0.976	0.60 (0.37 to 1.00)	0.05
Admission to stroke unit (n=495)	344 (69.4)	290 (76.9)	54 (45.4)	<0.001	4.21 (2.58 to 6.87)	<0.001

*Includes all consenting patients and patients who died during admission before consent was sought. †Includes patients who refused and from whom consent was not sought. ‡493 patients included in the logistic regression model. ¶P-value of the log likelihood ratio statistic (comparing the model with and without the variable). #Test for trend. **per unit increase in deprivation score.
LRT = likelihood ratio test; PACS = partial anterior circulation syndrome; LACS = lacunar stroke; POCS = posterior circulation syndrome; TACS = total anterior circulation syndrome; Uncertain = uncertain stroke type; TIA = transient ischaemic attack; IQR = interquartile range

Table 6.2 Characteristics of participants and non-participants amongst outpatients

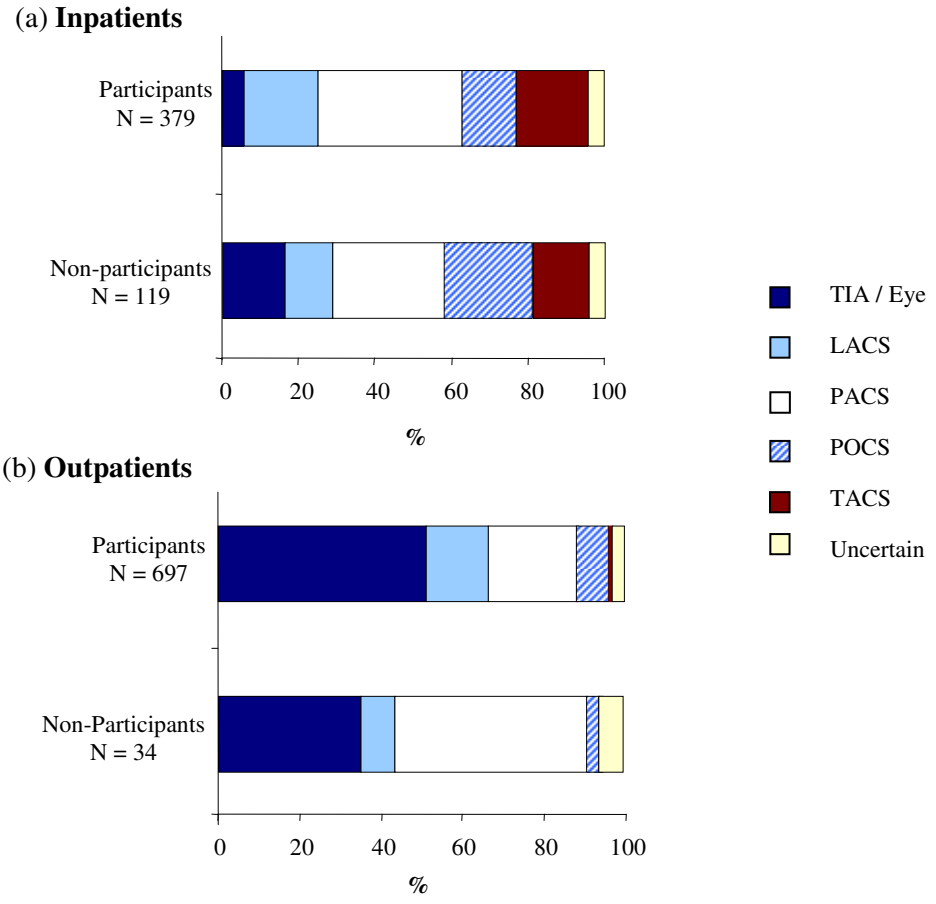
Characteristic	All patients (N = 731) n (%)	Participants* (N = 697) n (%)	Non-participants† (N = 34) n (%)	Unadjusted p-value	Adjusted OR participants vs non-participants (95% CI)‡	Adjusted p-value (LRT)¶
Mean age in years (± SD)	70 (± 11)	70 (± 11)	69 (± 12)	0.36	1.02 (0.98 to 1.05)	0.63
Male	395 (54)	378 (54)	17 (50)	0.63	1.00	0.72
Female	336 (46)	319 (46)	17 (50)		0.88 (0.42 to 1.81)	
Event type						
PACS	172 (23.5)	156 (22.4)	16 (47.1)	0.03	1.00	0.02
LACS	110 (15.0)	107(15.4)	3 (8.8)		13.6 (1.01 to 13.2)	
POCS	55 (7.5)	54 (7.8)	1 (2.9)		5.3 (0.7 to 41.9)**	
TACS	1 (0.1)	1 (0.1)	0 (0)		-	
Uncertain	23 (3.1)	21 (3.0)	2 (5.9)		1.0 (0.2 to 4.9)	
TIA / eye attack	370 (50.6)	358 (51.4)	12 (35.3)		3.2 (1.4 to 7.1)	
Socio-economic Deprivation score (N = 726)						
1 (most affluent)	80 (11.0)	78 (11.3)	2 (6.1)	0.04#	1.10 (0.86 to 1.42)††	0.45
2	131 (18.0)	120 (17.3)	11 (33.3)			
3	141 (19.0)	137 (19.8)	4 (12.1)			
4	191 (26.3)	182 (26.8)	9 (27.2)			
5	124 (17.1)	118 (17.0)	6 (18.2)			
6	41 (5.6)	41 (5.9)	0 (0)			
7 (least affluent)	18 (2.5)	17 (2.5)	1 (3.0)			

*Includes all consenting patients. †Includes patients who refused and from whom consent was not sought. ‡493 patients included in the logistic regression model. ¶P-value of the log likelihood ratio statistic (comparing the model with and without the variable). #Test for trend. **POCS and TACS combined for purpose of regression modelling. ††per unit increase in deprivation.
LRT = likelihood ratio test; PACS = partial anterior circulation syndrome; LACS = lacunar stroke; POCS = posterior circulation syndrome; TACS = total anterior circulation syndrome; Uncertain = uncertain stroke type; TIA = transient ischaemic attack.

Differences between participants and non-participants were less striking for outpatients, among whom the number and proportion of non-participants was small (34 / 731 = 5%; Figure 6.2, Table 6.2). The only statistically significant difference (in both univariate and adjusted analyses) between participants and non-participants among outpatients was in the distribution of event type (Figure 6.3, Table 6.2), with a lower proportion of mild cortical (partial anterior circulation) strokes among participants, but a greater proportion of lacunar and TIA patients.

The number of patients who refused consent (n = 11) was too small to perform any meaningful comparison of characteristics with consenters.

Figure 6.3 Distribution of event type by participation, for (a) inpatients and (b) outpatients



6.4.3 Are patients included in the ESS representative of all eligible patients?

Although there were some differences between participants and non-participants in the ESS, the high level of participation meant that, overall, participants were representative of all patients eligible for inclusion. The mean age of patients was almost identical, as was the proportion who were male, and there was very little difference in the distribution of event type (Table 6.3). Similarly, the distribution of socioeconomic deprivation scores was similar in both groups, and the length of stay among inpatients was identical. The only difference lay in the proportion of patients who were admitted to the stroke unit, with a higher proportion of participants having had stroke unit care compared with all eligible patients (77% vs 69%; Table 6.3).

Table 6.3 Comparison of characteristics of all eligible patients and all participants in the Edinburgh Stroke Study

Characteristic	All eligible patients (N = 1228) n (%)	All participants (N = 1075) n (%)
Mean age in years (± SD)	73.3 (± 12)	73.1 (± 12)
Male	621 (50.6)	554 (51.5)
Event type		
PACS	349 (28.4)	298 (27.7)
LACS	196 (16.0)	178 (16.6)
POCS	136 (11.1)	108 (10.1)
TACS	91 (7.4)	73 (6.8)
Uncertain type	45 (3.7)	38 (3.5)
TIA / eye attack	411 (33.5)	380 (35.4)
Socioeconomic deprivation score		
1 (most affluent)	126 (10.3)	115 (10.8)
2	233 (19.1)	204 (19.1)
3	234 (19.2)	208 (19.5)
4	309 (25.3)	269 (25.2)
5	209 (17.1)	180 (16.8)
6	60 (4.9)	54 (5.1)
7 (least affluent)	50 (4.1)	39 (3.7)
Median (IQR) length of hospital stay (inpatients only)	17 (5-46)	17 (5-44)
Admission to stroke unit (inpatients only)	344 (69)	290 (77)

Given the rather large proportion of outpatients included in the ESS the patients in our study are not, overall, be entirely representative of the stroke population within Edinburgh. Our study is somewhat over-representative of milder stroke events, and under-representative of more severe stroke events.

6.5 Discussion

Through comparing a subset of the Edinburgh Stroke Study population with a contemporaneous stroke audit not requiring explicit consent, we found that 88% of eligible patients identified in the audit participated in the ESS. Only a very small number of patients actually refused consent to be included in the ESS (1% of those approached for consent, and < 1% of eligible patients). The main cause of non-participation was our inability to seek consent from 9% of eligible patients. We did not routinely record reasons for non-inclusion of patients identified prospectively but from whom consent was not sought, but this information was available from our administrative records for some patients. Reasons for non-inclusion reflected the practical barriers to seeking consent, such as patients being discharged soon after admission before they could be approached for their consent, the difficulties in meeting with and obtaining consent from relatives of incapacitated patients, and the increased difficulty of obtaining consent from patients admitted to outlying wards, which is highlighted by the difference in the proportion of participants and non-participants admitted to the stroke unit. Almost all patients approached (99%) gave consent to use of their clinical data for research or contact with their family doctor, while only slightly fewer consented to questionnaire follow-up or storage of a blood sample for research analyses. Thus, the logistical hurdles associated with the

requirement to seek explicit consent, rather than patients' unwillingness to participate, was the main determinant of incomplete participation in the ESS.

The refusal rate in our study may have been minimised by the use of clear, brief, easily readable information leaflets and consent forms, and by consent being sought by doctors, on a background of good doctor-patient relationships. It may also partly reflect the patients' characteristics, including for example their age and cultural setting, as well as their perception of the seriousness of their condition and the need for research to improve our understanding of and treatments for stroke.

There is some evidence that the incomplete participation in the ESS, which can mainly be explained by the practicalities of the consent process itself, introduced potential bias, with important differences between participants and non-participants. Participants were more likely than non-participants to be outpatients, and so to have milder events, since it was relatively straightforward to seek consent from outpatients as a standard part of the clinic procedure, and more difficult to streamline the process for inpatients. Inpatient participants were more likely than non-participants to be admitted to a stroke unit, an intervention which leads to better outcomes, as demonstrated in randomised controlled trials (Stroke Unit Trialists' Collaboration 2001), reflecting the practical difficulties of obtaining consent from patients admitted to outlying wards in different parts of the hospital. The smaller proportion of TIA patients among inpatient participants reflects the difficulties in obtaining consent from patients with very mild events, who are often admitted to hospital for a short time only. The larger proportion of milder (lacunar and partial anterior circulation) strokes among inpatient participants compared with non-participants suggests that it was easier to obtain consent from patients with milder events, who were likely to be

admitted for a long enough duration to be approached for their consent, and then to be able to consent for themselves, rather than having to wait for a relative to be available. The larger proportion of inpatients with very severe (total anterior circulation) strokes among participants could be explained by their relatively high early case fatality (Bamford *et al*. 1991) coupled with our ability to include in our study those patients who died in hospital before consent could be sought. Although there were statistically significant differences in the distribution of events among outpatients for participants versus non-participants, these did not follow an easily explainable pattern, perhaps because events among outpatients were mostly mild, and the number of non-participants (n = 34) was small.

Although there were some differences in the characteristics of participants and non-participants, the high level of participation meant that participants (inpatients and outpatients combined) were still representative of all eligible patients. This indicates that our study cohort is likely to be very representative of the target population of all stroke and TIA patients seen at or admitted to our hospital. The only potentially important difference was the higher proportion of patients admitted from the stroke unit among participants compared with all eligible patients, which indicates that we have underrepresented patients who were admitted to our hospital but not managed in the stroke unit.

6.5.1 Limitations

My comparisons with the clinical stroke audit were limited by the data available in the audit. Firstly, the baseline characteristics that I could compare between participants and non-participants were restricted to variables collected by both the audit and the ESS, using comparable methods and definitions. Secondly, I was

unable to assess whether there were any differences in outcome between participants and non-participants, since patients identified by the audit are not routinely followed for further events.

6.5.2 Comparisons with previous studies

Several other groups have reported on the practical difficulties of obtaining consent in various clinical epidemiological settings, important baseline differences between consenters and non-consenters, and serious outcome bias as a result of the requirement for explicit consent (Al-Shahi *et al*. 2005; Iversen A *et al*. 2006; McKinney *et al*. 2005; Tu *et al*. 2004; Ward *et al*. 2004). One other study has investigated patient participation in a hospital-based stroke register. This was a multicentre Canadian study, in which the target population was all inpatient admissions for stroke (Tu *et al*. 2004). The refusal rate (12% of eligible patients) was much higher and the overall proportion of eligible patients included (51%) considerably lower than in the ESS, even compared with only the inpatients in the ESS (76% of whom were included). These differences could have been due to: the added complexities of obtaining consent in a multicentre register compared with a single centre study; variation between the studies in the administrative demands of the consent process, and the resources available to meet them; research nurses rather than doctors seeking consent in the Canadian study; and perhaps cultural differences between the Scottish and Canadian populations. Notwithstanding the differences, the Canadian study also demonstrated that the practical difficulties in obtaining consent rather than explicit refusal was the main determinant of incomplete participation, and found differences between participants and non-participants in baseline

characteristics and in-hospital mortality, suggesting that participants had milder strokes.

6.5.3 Conclusion

Very few patients refused to be included in the Edinburgh Stroke Study, but processes integral to the requirement for explicit consent reduced participation, most noticeably among patients admitted to hospital. However, the high level of participation meant that there was little difference in most baseline characteristics studied, between those eligible for inclusion in the stroke study and those who actually participated in the study.

C. Analyses of individual patient data, including Edinburgh Stroke Study Data

Chapter 7. Risk factors for lacunar versus non-lacunar ischaemic stroke: a pooled individual patient data analysis

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7.1 Aim

In this chapter I will present the results of a collaborative project in which I pooled individual patient data from five stroke registers and compared the risk factor profiles of patients with lacunar versus non-lacunar ischaemic stroke.

In my analyses, I aimed to:

- determine risk factor-ischaemic stroke subtype associations for each stroke register individually before pooling the data and adjusting for register; register, age and sex; register, age, sex and other risk factors;
- perform a series of sensitivity analyses to determine the robustness of the results of the primary analysis to alteration of the comparison groups, to assess how choice of comparison group affects the results;
- estimate the extent of misclassification of ischaemic stroke subtypes among patients included in the two Edinburgh-based stroke registers;
- update my previous meta-analysis (presented in chapter 3) to include both the individual stroke registers analysed here and existing published studies that used similar unbiased methods of classifying ischaemic stroke subtypes.

7.2 Introduction

In my systematic review and meta-analysis of published observational studies, I found some differences in the risk factor profiles of patients with lacunar compared with non-lacunar ischaemic stroke when I considered only those studies that had used risk factor-independent methods of classifying ischaemic stroke subtypes. In these studies I found no excess of diabetes, and a slight significant excess of hypertension in lacunar versus non-lacunar ischaemic stroke, thus challenging the widely held belief that both hypertension and diabetes are more common in lacunar than non-lacunar ischaemic stroke. I did find a higher prevalence of atrial fibrillation and carotid stenosis in patients with non-lacunar compared with lacunar ischaemic stroke. A lower prevalence of carotid stenosis among patients with lacunar ischaemic stroke might reflect a lower prevalence of systemic atherosclerosis in these patients. A lower prevalence of ischaemic heart disease (IHD), a marker of systemic atherosclerosis, among patients with lacunar ischaemic stroke would further support the notion of a non-atherothrombotic lacunar arterial pathology. However, although there may have been a trend towards a lower prevalence of IHD among patients with lacunar stroke, the confidence interval was compatible with there being no difference in the prevalence of this risk factor between patients with lacunar versus non-lacunar ischaemic stroke.

Although I included data from 10 studies (6706 patients) that used a clinical and imaging-based ischaemic stroke classification method in my meta-analysis, which allowed for reasonable precision, my results were based on univariate analyses for each risk factor studied, and not adjusted for the potential confounding effects of age, sex and other vascular risk factors. Furthermore, the definitions of risk factors and of

the non-lacunar comparison group varied between studies, and data on several risk factors were sparse.

I was able to overcome these shortcomings by pooling data from the ESS with individual patient data from four collaborating prospective stroke registers that recruited from predominantly Caucasian populations between 1990 and 2005, and that used identical risk factor-independent methods of classifying ischaemic stroke subtypes to the ESS, and consistent risk factor definitions. I performed both univariate and multivariable risk factor comparisons between lacunar and non-lacunar ischaemic stroke, and assessed the effects of varying the lacunar and non-lacunar comparison groups through a series of pre-defined sensitivity analyses. I also updated my previous systematic review to incorporate the unadjusted data from the collaborating stroke registers.

7.3 Methods

7.3.1 Obtaining and preparing data from stroke registers

In addition to the baseline data from the ESS, we obtained individual patient data on all patients with stroke from the Lothian Stroke Register (LSR) (Wardlaw *et al*. 1998), which recruited from the same target population as the ESS during an earlier time period, and three community-based stroke registers in Perth, Australia (Jamrozik *et al*. 1999), and in Lund (Lindgren *et al*. 1994a) and Orebro (Appelros *et al*. 2003) in Sweden. Appropriate ethical approval had been sought and obtained for each register. In each of these additional registers a stroke specialist clinician assessed patients as soon as possible after the stroke, with prospective recording of demographic and clinical details, including exposure to vascular risk factors and results of brain imaging and other investigations.

After receiving data on requested items from each study, we converted all individual patient data to a common format (AH and CLMS), ran a series of data checks for completeness and consistency (AH), resolved any queries and inconsistencies with the investigators from each study (CLMS) and made corrections where necessary.

7.3.2 Classification of ischaemic stroke subtypes

In my analyses I included all patients with a clinically evident stroke demonstrated to be ischaemic by the absence of recent intracerebral haemorrhage on CT or MR brain imaging, or at autopsy. As in the ESS, each of the other stroke registers had used the OCSP classification (Bamford *et al*. 1991) to assign a clinical stroke syndrome and provided data on the presence and location of any visible relevant infarct(s) on brain imaging or at autopsy. Following the same procedure that we used in the ESS (described in detail earlier), we modified the final ischaemic stroke subtype classification if an infarct considered relevant to the presenting stroke was present on brain imaging or at autopsy, leading to a final classification of TACI, PACI, LACI, POCI or uncertain ischaemic subtype.

7.3.3 Risk factor definitions

We defined hypertension as a history of treated hypertension prior to the stroke; diabetes as previously diagnosed with - or on medication for - type I or type II diabetes mellitus; and ischaemic heart disease as a prior history of myocardial infarction, angina or coronary revascularisation. We considered a cardioembolic source to be present if a patient had a clear history or post-stroke electrocardiogram evidence of paroxysmal or persistent atrial fibrillation. I dichotomised cigarette smoking into current or ex-smoker of ≤12 months, and never or ex-smoker of > 12 months. We defined excess alcohol intake in women as > 14 units per week, and in

men as > 21 units per week. We defined carotid stenosis as ≥ 70% stenosis (European Carotid Surgery Trial criteria) on any imaging investigation of the extracranial neck arteries (predominantly ultrasound, but in some cases, MR, CT or digital subtraction angiography).

7.3.4 Statistical analyses

I performed statistical analyses using STATA version 8.0 (StataCorp 2003).

7.3.4.1 Primary analyses

In the primary analysis I included all patients with a first-ever-in-a-lifetime anterior circulation ischaemic stroke, and compared risk factors among patients with a lacunar (LACI) versus those with a non-lacunar (PACI or TACI) ischaemic stroke. The POCI group comprised a mixture of posterior circulation lacunar and non-lacunar ischaemic stroke. Because we could not reliably distinguish between these, I excluded all patients with POCI from the primary analysis.

7.3.4.2 Unadjusted analyses

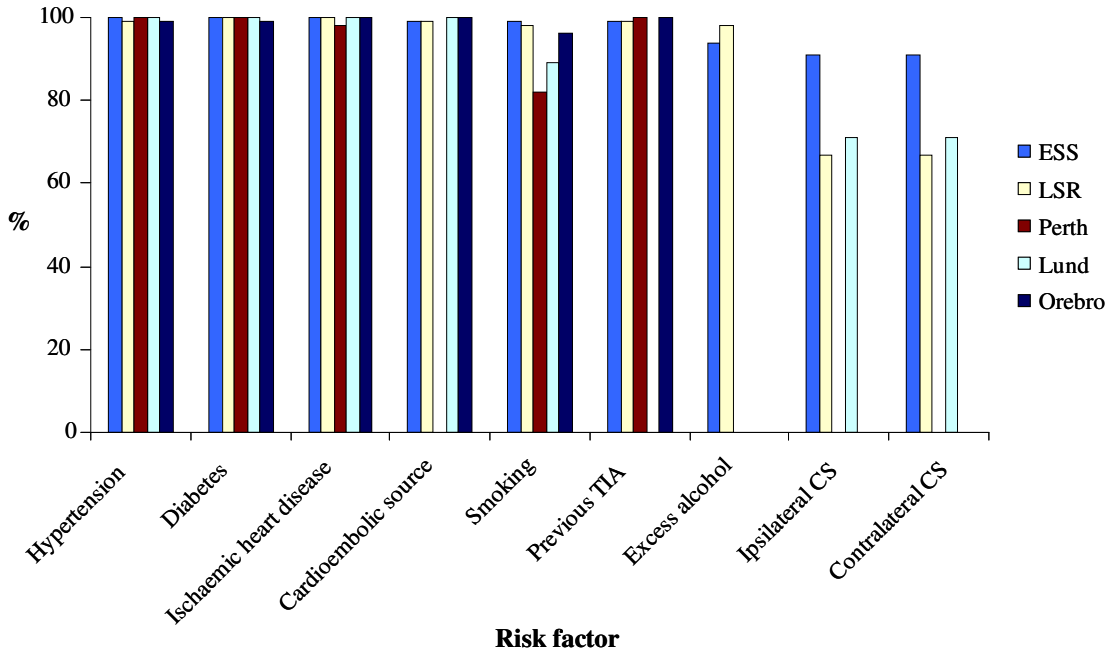
I determined the crude association between each risk factor and ischaemic stroke subtype, comparing lacunar versus non-lacunar ischaemic stroke. I obtained study-specific and Mantel-Haenszel fixed effect pooled odds ratios (ORs) and their 95% confidence intervals, assessing heterogeneity between registers using the I^2 statistic (Higgins & Thompson 2002). I used Student's t-test to compare mean ages and the χ^2 test to compare proportions of patients who were male.

7.3.4.3 Adjusted analyses

I used logistic regression to obtain adjusted ORs, using data from the ESS and LSR only, since data was not available on all risk factors in the other three studies (Figure 7.1). First, I adjusted risk factor associations for register, and then for register, age

and sex. In a fully adjusted model, I adjusted for register, age, sex, and each of the other risk factors under study.

Figure 7.1 Proportion of patients with data on each risk factor, by study



TIA = transient ischaemic attack; CS = carotid stenosis; ESS = Edinburgh Stroke Study; LSR = Lothian Stroke Register

Among patients included in the ESS and LSR, data on most risk factors were present for 98-100% of patients. Data on ipsilateral and contralateral carotid stenosis were rather less complete, being present for 91% of patients (94% of lacunar patients and 89% of non-lacunar patients) in the ESS and 67% of patients (71% of lacunar patients and 64% of non-lacunar patients) in the LSR. Patients for whom data was not present for all relevant risk factors did not differ significantly in terms of age, sex

and frequency of other risk factors when compared with patients for whom risk factor data was complete. The one exception was cardioembolic source, which was statistically significantly less prevalent among those in whom all risk factor data was available compared with those in whom some risk factor data was missing (17% vs 25%; $p < 0.001$). This was related to whether or not data on carotid stenosis had been collected, with patients who had a cardioembolic source less likely to have had imaging investigation of the extracranial arteries for carotid stenosis. In my logistic regression model I excluded from each adjusted model 652 of the total 2348 patients (28%) for whom data was missing for one or more of the included risk factors (which left 1696 patients). Because carotid stenosis was the only variable missing in a substantial number of patients, I also repeated my logistic regression analysis but excluded ipsilateral and contralateral stenosis from the model, thereby excluding only 104 (4%) of the total 2348 patients. The results from this model were very similar to those from the model including the carotid stenosis variables, so I have presented the results of the latter model only.

I investigated interaction between each risk factor and each of age and sex, by introducing interaction terms into the model, using the log likelihood ratio test to assess for significant interaction.

7.3.5 Sensitivity analyses

To test the robustness of the primary analysis results and to determine whether the choice of comparison groups has an effect on the results, I repeated the above unadjusted and adjusted analyses in four pre-defined sensitivity analyses:

(1) LACI versus PACI or TACI for all patients with at least one ischaemic stroke, whether first-ever-in-a-lifetime or recurrent stroke;

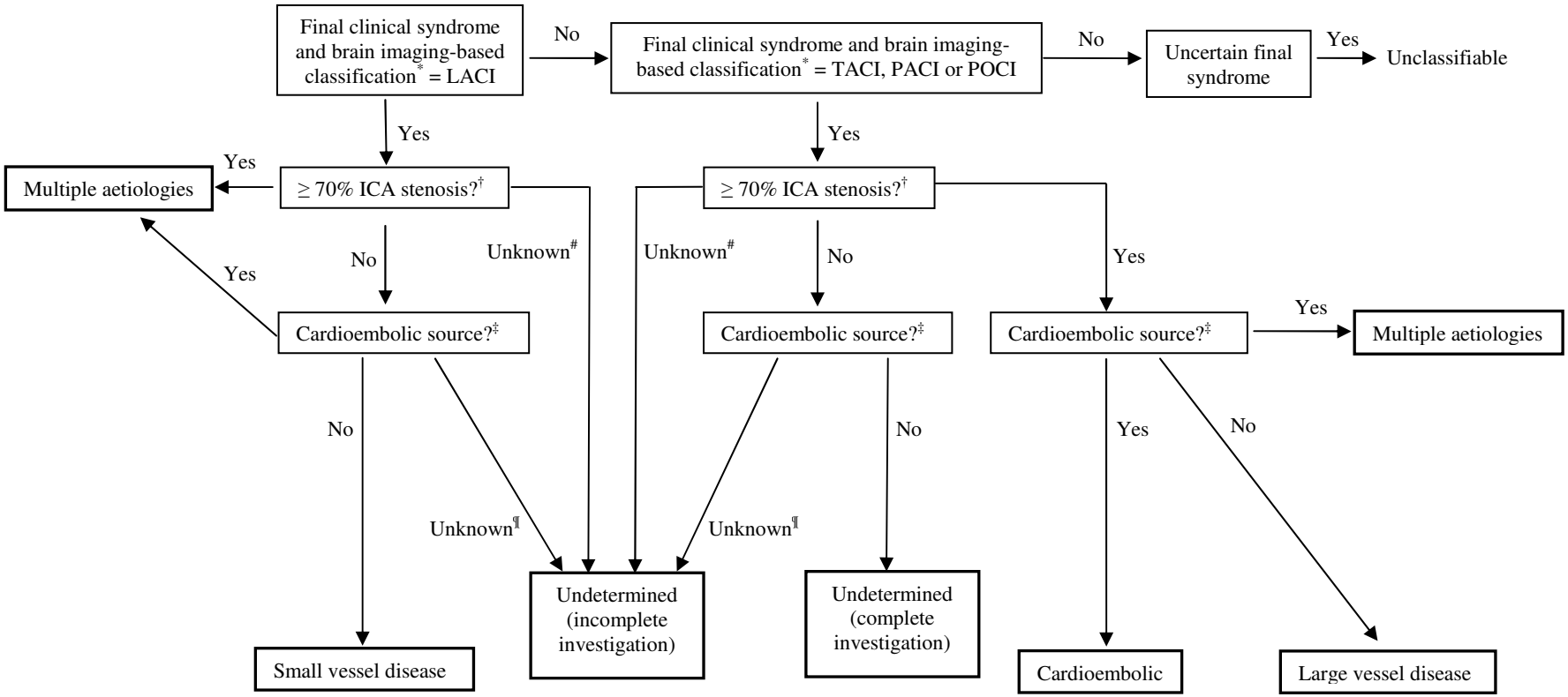
(2) LACI versus PACI or TACI among all patients with a first-ever ischaemic stroke, excluding those with a potential cardioembolic source;

(3) LACI versus PACI, TACI or POCI among all patients with a first-ever ischaemic stroke;

(4) small vessel versus large vessel ischaemic stroke among all patients with an anterior circulation first-ever ischaemic stroke.

For the last comparison I devised an algorithm based on the TOAST classification (Adams *et al*. 1993) to assign a presumed aetiological cause of stroke to each patient. In addition to the classification based on the clinical syndrome and brain imaging, the algorithm took into account the carotid imaging results, and presence or absence of a cardioembolic source, but was independent of hypertension, diabetes or any other vascular risk factors (Figure 7.2).

Figure 7.2 Modified TOAST algorithm used to assign aetiological ischaemic stroke subtypes



*LACI = lacunar infarction; PACI = partial anterior circulation infarction; TACI = total anterior circulation infarction; POCI = posterior circulation infarction †Ipsilateral internal carotid artery stenosis. ‡Cardioembolic source defined as history of or post-stroke electrocardiogram (+/- echocardiogram) evidence of atrial fibrillation or cardiac valve disease. #Imaging of extracranial neck arteries not performed. ¶Appropriate cardiac investigation (electrocardiogram +/- echocardiogram) not performed in patients with no known history of atrial fibrillation.

7.3.6 Estimating extent of misclassification of ischaemic stroke subtypes

I estimated the extent of misclassification of ischaemic stroke subtype in the primary analysis by calculating the proportion of patients with a visible relevant infarct on their brain scan whose final classification placed them in a different comparison group (i.e. lacunar or non-lacunar) from their classification based on the clinical syndrome alone. I then applied this proportion to the patients who had no visible relevant infarct on brain imaging to estimate the number (and proportion) of patients in the analysis who were residually misclassified.

In a post-hoc analysis, I also repeated my primary analysis among patients with a visible relevant infarct only, to assess the effects of excluding all potentially misclassified patients.

7.3.7 Updated meta-analysis to include individual patient data

I updated my previous meta-analysis to pool unadjusted data from the primary analysis of my individual patient data pooling project (using data from all five stroke registers) with data extracted from those previously identified published studies that had used a similar clinical and imaging-based (but risk factor-independent) method for classifying subtypes of ischaemic stroke. I used Cochrane Review Manager (Cochrane Collaboration 2003) to determine study-specific and Mantel Haenszel fixed effect pooled ORs, assessing heterogeneity between studies using the I^2 statistic.

7.4 Results

7.4.1 Characteristics of stroke registers included in the pooled individual patient data analysis

Between them, the five registers contributed data on 5101 patients with at least one stroke. Of these, 429 (8%) did not have either brain imaging or autopsy performed (or these data were not available) and 414 had had a spontaneous intracerebral haemorrhage. In total there were 4258 patients with a brain imaging-confirmed ischaemic stroke, and of these 3593 had a first-ever-in-a-lifetime ischaemic stroke. After excluding 638 patients with a POCI and 80 with an uncertain clinical syndrome, 2875 patients - 1062 with lacunar and 1813 with non-lacunar ischaemic stroke - were included in the primary analyses. The Lothian Stroke Register and the ESS were the largest studies, contributing 1510 and 838 patients respectively to the primary analyses, 82% of the total data (Tables 7.1 and 7.2).

The Lothian stroke register recruited from the same source of patients as the ESS, that is inpatient admissions and outpatient clinics at the Western General Hospital, during an earlier time period, and the other three registers were community-based. The mean age of patients in the five registers ranged from 67 to 76 years. Patients in the hospital-based registers were slightly younger than in the community-based ones, and overall lacunar patients were slightly younger than non-lacunar patients (mean 68 versus 71 years, $p < 0.001$). There were approximately equal numbers of men and women in the non-lacunar group, but slightly more men (58%) than women in the lacunar group ($p < 0.001$). The proportion of lacunar and non-lacunar cases was very similar in the different registers, with lacunar cases comprising 32% to 42% of anterior circulation ischaemic strokes (Table 7.1).

Table 7.1 Description and baseline characteristics of registers included in the individual patient data analysis

Study	Period of recruitment	Stroke population	Number of patients with anterior circulation ischaemic stroke (lacunar : non-lacunar)	Age* (lacunar : non-lacunar)	Gender (% male) (lacunar : non-lacunar)	Brain imaging†	
						CT (%)	MRI (%)
Edinburgh Stroke Study	2002-2005	Consecutive consenting stroke patients admitted to or seen in outpatient clinics at the Western General Hospital, Edinburgh	838 (285 : 553)	71 ± 13 (69 ± 12 : 72 ± 13)	51 (60 : 47)	81	19
Lothian Stroke Register	1990-2000	Consecutive patients admitted to or seen in outpatient clinics at the Western General Hospital, Edinburgh	1510 (565 : 945)	67 ± 13 (66 ± 12 : 68 ± 14)	53 (59 : 50)	90	10
Perth (Australia)	1995-1996	Community-based study based on a defined geographical area in the northern suburbs of Perth. Stroke patients were identified using multiple methods of ascertainment	126 (40 : 86)	76 ± 13 (77 ± 13 : 76 ± 13)	52 (48 : 53)	81	1
Lund (Sweden)	1991-1992	Community-based study which registered all new stroke patients living in the catchment area of Lund University Hospital. Patients were identified using multiple methods of ascertainment	147 (66 : 81)	75 ± 11 (73 ± 12 : 76 ± 10)	56 (64 :51)	88	10
Orebro (Sweden)	1999-2000	Community-based study which registered all new stroke cases in Orebro using multiple overlapping methods of ascertainment	254 (106 : 148)	75 ± 11 (75 ± 10 : 76 ± 12)	45 (48 : 43)	99	1

*Mean ± standard deviation
†Type of brain imaging used to determine final ischaemic stroke subtype classification. Where % does not add up to 100, remainder of patients had an autopsy

Table 7.2 Frequency of risk factors among lacunar and non-lacunar patients, by study

Characteristic*	All studies† (N = 2875)		Study‡									
			ESS (N = 838)		LSR (N = 1510)		Perth (N = 126)		Lund (N = 147)		Orebro (N = 254)	
	Lacunar (N = 1062) n / N	Non-lacunar (N = 1813) n / N	Lacunar (N = 285) n / N (%)	Non-lacunar (N = 553) n / N (%)	Lacunar (N = 565) n / N	Non-lacunar (N = 945) n / N	Lacunar (N = 40) n / N	Non-lacunar (N = 86) n / N	Lacunar (N = 66) n / N	Non-lacunar (N = 81) n / N	Lacunar (N = 106) n / N	Non-lacunar (N = 148) n / N
Median days to brain scan (IQR) (N=2845)	6 (2-21)	2 (1-13)	9 (2-24)	2 (1-13)	12 (2-23)	4 (1-19)	3 (1-6)	2 (0-4)	6 (2-12)	4 (1-7)	12 (2-23)	2 (1-3)
Ischaemic heart disease (N=2875)	231 / 1062 (22)	550 / 1811 (30)	56 / 285 (20)	151 / 553 (27)	110 / 565 (19)	264 / 945 (28)	12 / 40 (30)	32 / 84 (38)	26 / 66 (39)	50 / 81 (62)	27 / 106 (25)	53 / 148 (36)
Cardioembolic source (N=2745)	106 / 1020 (10)	445 / 1725 (26)	39 / 284 (14)	161 / 551 (29)	35 / 564 (6)	214 / 945 (23)	No data		12 / 66 (18)	28 / 81 (35)	20 / 106 (19)	42 / 148 (28)
Hypertension (N=2867)	441 / 1062 (42)	793 / 1805 (44)	135 / 285 (47)	287 / 553 (52)	222 / 565 (39)	381 / 941 (40)	26 / 40 (65)	51 / 86 (60)	14 / 66 (21)	24 / 81 (30)	44 /106 (42)	50 / 144 (35)
Diabetes (N=2872)	136 / 1062 (13)	215 / 1810 (12)	36 / 285 (13)	57 / 553 (10)	64 / 565 (11)	106 / 945 (11)	8 / 40 (20)	12 / 86 (14)	8 / 66 (12)	13 / 81 (16)	20 /106 (19)	27 / 145 (19)
Ipsilateral ICA stenosis (N=1874)	48 / 721 (7)	256 / 1153 (22)	12 / 267 (5)	94 / 494 (19)	30 / 401 (7)	150 / 608 (25)	No data		6 / 53 (11)	12 / 51 (24)	No data	
Contralateral ICS stenosis (N=1878)	32 / 722 (4)	96 / 1156 (8)	12 / 267 (5)	31 / 495 (6)	18 / 402 (4)	62 / 610 (10)	No data		2 / 53 (4)	3 / 51 (6)	No data	
Previous TIA (N=2719)	140 / 993 (14)	285 / 1726 (17)	48 / 285 (17)	101 / 551 (18)	74 / 562 (13)	139 / 941 (15)	6 / 40 (15)	17 / 86 (20)	No data		12 / 106 (11)	28 / 148 (19)
Smoking (N=2792)	432 / 1041 (41)	563 / 1751 (32)	111 / 283 (39)	158 / 545 (29)	254 / 561 (45)	339 / 925 (37)	6 / 32 (19)	14 / 71 (20)	28 / 60 (47)	23 / 71 (32)	33 / 105 (31)	29 / 139 (21)
Alcohol excess (N=2267)	142 / 831 (17)	187 / 1436 (13)	49 / 273 (18)	65 / 511 (13)	93 / 558 (17)	122 / 925 (13)	No data		No data		No data	

*N = total number of patients in all studies (ESS, LSR, Perth, Lund and Orebro) with available data for each risk factor
†Number (percentage) of patients with each risk factor in the lacunar and non-lacunar groups, for all studies
‡Number (percentage) of patients with each risk factor in the lacunar and non-lacunar groups, by study
IQR = interquartile range; ESS = Edinburgh Stroke Study; LSR = Lothian Stroke Register

In all registers combined, the median time from onset of stroke symptoms to brain imaging was 6 days (interquartile range 2-21) among patients with lacunar ischaemic stroke and 2 days (interquartile range 1-13) among patients with non-lacunar ischaemic stroke (Table 7.2). All five registers provided data on hypertension, diabetes, ischaemic heart disease, and smoking. For the remaining risk factors, data was not available from *all* registers (Figure 7.1 & Table 7.2).

7.4.2 Risk factor-ischaemic stroke subtype associations

For each risk factor, the register-specific univariate ORs (lacunar versus non-lacunar ischaemic stroke) were generally very similar across all registers, with very little or no between-register heterogeneity, except for cardioembolic source, for which there was substantial heterogeneity (Figure 7.3).

Using only data from the Edinburgh registers, univariate pooled analyses adjusted for register and fully adjusted pooled analyses generally yielded very similar results. A history of ischaemic heart disease was less common in lacunar patients, with the odds of ischaemic heart disease reduced by about a quarter in lacunar compared with non-lacunar patients (fully adjusted OR 0.74; 95% CI 0.57 to 0.96; Figure 7.4). The odds of having a cardioembolic source was also reduced by about two-thirds in lacunar compared with non-lacunar patients, which again persisted after fully adjusting for confounding factors (OR 0.33; 95% CI 0.24 to 0.47; Figure 7.4). The odds of severe ipsilateral carotid stenosis was reduced by about 80% in lacunar compared with non-lacunar patients (OR 0.21; 95% CI 0.15 to 0.30; Figure 7.4).

Figure 7.3 Univariate odds ratios (lacunar versus non-lacunar) for risk factors, by register

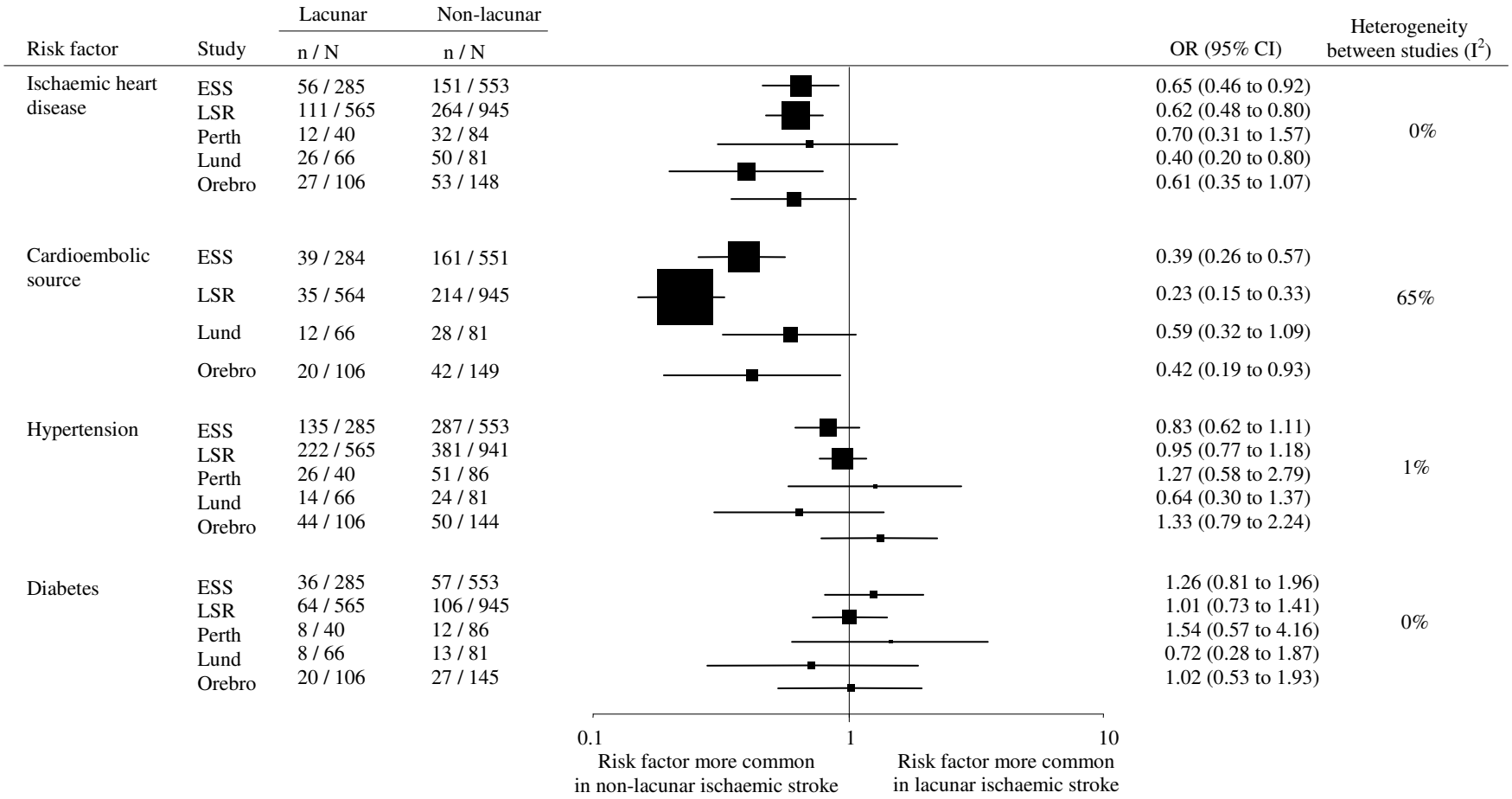


Figure 7.3 continued

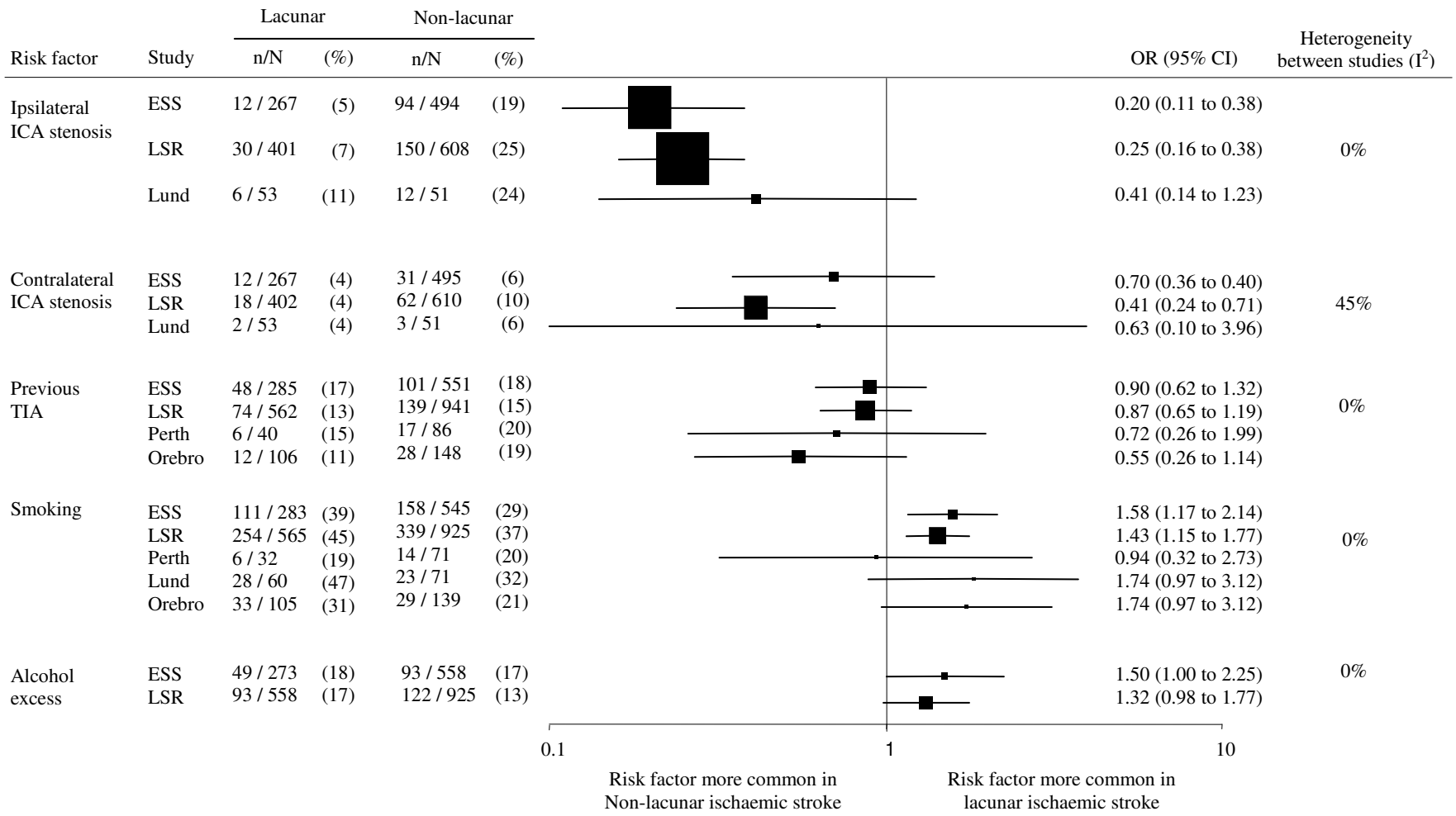


Figure 7.4 Pooled univariate and multivariate odds ratios (lacunar versus non-lacunar) for risk factors (including data from Edinburgh studies only)

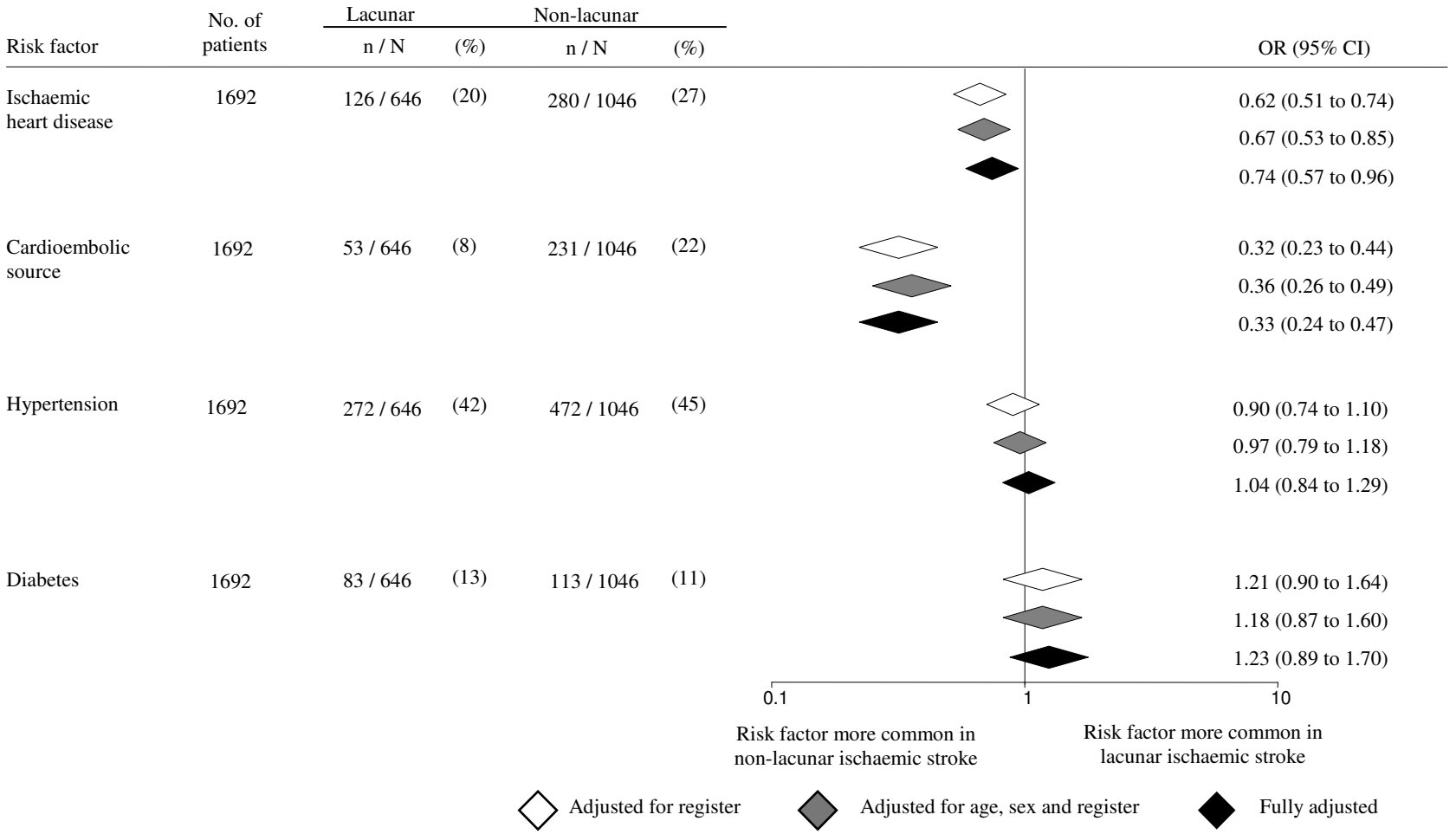
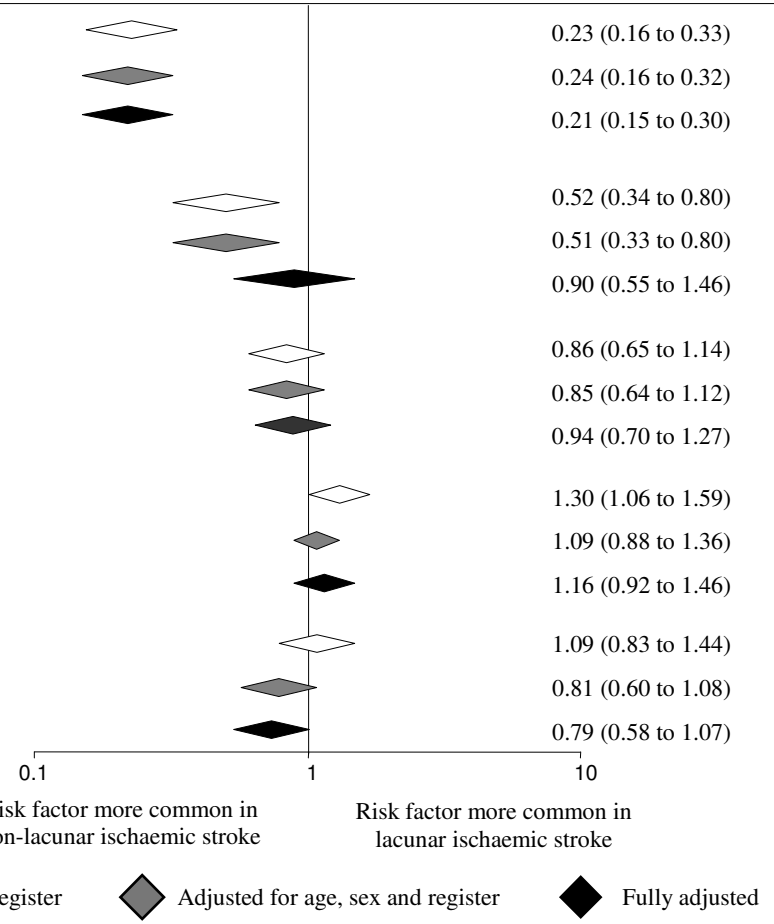


Figure 7.4 continued

Risk factor	No. of Patients	Lacunar (n / N)	Lacunar (%)	Non-lacunar (n / N)	Non-lacunar (%)	OR (95% CI)
Ipsilateral ICA stenosis	1692	41 / 646	(6)	231 / 1046	(22)	0.23 (0.16 to 0.33)
						0.24 (0.16 to 0.32)
						0.21 (0.15 to 0.30)
Contralateral ICA stenosis	1692	29 / 646	(4)	85 / 1046	(8)	0.52 (0.34 to 0.80)
						0.51 (0.33 to 0.80)
						0.90 (0.55 to 1.46)
Previous TIA	1692	89 / 646	(14)	166 / 1046	(16)	0.86 (0.65 to 1.14)
						0.85 (0.64 to 1.12)
						0.94 (0.70 to 1.27)
Smoking	1692	273 / 646	(42)	375 / 1046	(36)	1.30 (1.06 to 1.59)
						1.09 (0.88 to 1.36)
						1.16 (0.92 to 1.46)
Alcohol excess	1692	99 / 646	(15)	148 / 1046	(14)	1.09 (0.83 to 1.44)
						0.81 (0.60 to 1.08)
						0.79 (0.58 to 1.07)



After adjusting for age, sex and other risk factors, there was no significant difference in the frequency of contralateral carotid stenosis (which presumably does not remain independently associated with ischaemic stroke subtype because of its close correlation with ipsilateral stenosis). Neither hypertension nor diabetes was associated more with either lacunar or non-lacunar ischaemic stroke, with the lack of association persisting after adjustment for age, sex and other risk factors (OR 1.04; 95% CI 0.84 to 1.29 and OR 1.23; 95% CI 0.89 to 1.70, respectively; Figure 7.4). Similarly, prior TIA and excess alcohol were not associated more with either lacunar or non-lacunar ischaemic stroke. Smoking appeared to be more common in patients with lacunar compared with non-lacunar ischaemic stroke but this association did not persist in the fully adjusted model (Figure 7.4).

There was no evidence of interaction by age or sex for each of the risk factor-ischaemic stroke subtype associations.

7.4.3 Sensitivity analyses

In the first three planned sensitivity analyses, I obtained very similar results to the primary analyses (Table 7.3). The results were unaffected by inclusion of both recurrent and first-ever strokes; inclusion of patients with posterior circulation ischaemic stroke in the non-lacunar comparison group; or exclusion of patients with a cardioembolic source from both comparison groups.

When I compared patients whose ischaemic stroke was attributed to small versus large vessel disease, having applied my modified TOAST algorithm, I did find some apparent differences from the results of the primary analysis: contralateral carotid artery stenosis was much more common in ischaemic strokes attributed to large vessel disease in both unadjusted and adjusted analyses, but this was presumably

because of a correlation with ipsilateral stenosis which was not adjusted for due to its inclusion in the TOAST subtype definitions; smoking also appeared commoner in large vessel disease (Table 7.3). However, the analysis of TOAST subtypes was based on a smaller number of patients which reduced precision of the results as demonstrated by the relatively wide confidence intervals for all estimates. These analyses included a smaller number of patients from the ESS and LSR than in the other analyses because an aetiological classification could not be assigned to every patient, with the cause of stroke in a rather large proportion of patients remaining undetermined (Table 7.4). Where we classified patients as having an ischaemic stroke of undetermined aetiology, we categorised them further as having had complete or incomplete investigation (Figure 7.2). Thus, where patients had undergone imaging of the extracranial neck arteries to determine presence of internal carotid artery stenosis, and ECG or ECHO to determine presence of atrial fibrillation (the main source of cardiac emboli in stroke patients), but were found not to have severe stenosis or cardiac sources of emboli, we classified them as having had a stroke of "undetermined aetiology - complete investigation". We considered patients in whom cardiac investigations or imaging of the extracranial neck arteries were not performed as having had an ischaemic stroke of "undetermined aetiology - incomplete investigation". More patients in the LSR than the ESS were categorised as having an undetermined stroke subtype due to incomplete investigation, largely because fewer patients in the LSR had carotid doppler ultrasound of the extracranial neck arteries (Table 7.4).

I also re-classified patients using this same method, but defined severe stenosis as presence of an ipsilateral carotid stenosis ≥ 50% instead of ≥ 70%. After re-

classifying patients, the proportion of patients in the small vessel disease category was slightly lower, as some patients with 50-69% carotid artery stenosis were classed as having multiple aetiologies. The proportion of patients in the large vessel disease category increased, as patients with 50-69% carotid artery stenosis previously classed as having an undetermined cause of stroke despite complete investigation were re-classified as having large vessel disease. However, the proportion of patients classified as having an undetermined cause despite complete investigation was still relatively high (23%), and only marginally lower than when I used a severe carotid stenosis definition of ≥ 70% ipsilateral carotid stenosis (27%). When I then repeated my primary analyses using my modified TOAST algorithm which incorporated this less strict definition of severe carotid stenosis, I obtained very similar results to those in the primary analysis and in my first modified TOAST classification sensitivity analysis.

Table 7.3 Sensitivity analyses: unadjusted and adjusted odds ratios*

Risk factor	Analysis	Total patients in analyses	OR (95% CI) Adjusted for register	OR (95% CI) Fully adjusted†
Ischaemic heart disease	Primary	1692	0.67 (0.53 to 0.85)	0.74 (0.57 to 0.96)
	All strokes included	2013	0.63 (0.51 to 0.78)	0.71 (0.56 to 0.89)
	POCI included	2132	0.70 (0.56 to 0.87)	0.76 (0.60 to 0.96)
	Cardioembolic excluded	1408	0.74 (0.57 to 0.96)	0.76 (0.58 to 1.01)
	Modified TOAST	759	0.64 (0.44 to 0.95)	0.75 (0.49 to 1.14)
Cardioembolic source	Primary	1692	0.33 (0.23 to 0.44)	0.33 (0.24 to 0.47)
	All strokes included	2013	0.36 (0.28 to 0.48)	0.40 (0.30 to 0.53)
	POCI included	2132	0.35 (0.26 to 0.48)	0.38 (0.27 to 0.52)
	Modified TOAST‡	-	-	-
Hypertension	Primary	1692	0.90 (0.74 to 1.10)	1.04 (0.84 to 1.29)
	All strokes included	2013	0.88 (0.74 to 1.06)	1.02 (0.84 to 1.24)
	POCI included	2132	0.90 (0.75 to 1.09)	0.99 (0.81 to 1.21)
	Cardioembolic excluded	1408	0.93 (0.74 to 1.15)	1.03 (0.81 to 1.29)
	Modified TOAST	759	0.77 (0.56 to 1.06)	0.86 (0.60 to 1.23)
Diabetes	Primary	1692	1.21 (0.90 to 1.64)	1.23 (0.89 to 1.70)
	All strokes included	2013	1.17 (0.89 to 1.53)	1.23 (0.92 to 1.64)
	POCI included	2132	1.22 (0.92 to 1.62)	1.24 (0.92 to 1.67)
	Cardioembolic excluded	1408	1.24 (0.89 to 1.73)	1.20 (0.84 to 1.70)
	Modified TOAST	759	1.41 (0.82 to 2.44)	1.28 (0.71 to 2.30)
Ipsilateral ICA stenosis	Primary	1692	0.23 (0.16 to 0.33)	0.21 (0.14 to 0.30)
	All strokes included	2013	0.26 (0.20 to 0.36)	0.24 (0.17 to 0.33)
	POCI included	2132	0.35 (0.25 to 0.49)	0.31 (0.21 to 0.44)
	Cardioembolic excluded	1408	0.20 (0.14 to 0.29)	0.20 (0.14 to 0.29)
	Modified TOAST‡	-	-	-
Contralateral ICA stenosis	Primary	1692	0.52 (0.34 to 0.80)	0.90 (0.55 to 1.46)
	All strokes included	2013	0.57 (0.39 to 0.83)	1.00 (0.66 to 1.52)
	POCI included	2132	0.70 (0.46 to 1.08)	1.09 (0.68 to 1.75)
	Cardioembolic excluded	1408	0.49 (0.31 to 0.78)	0.89 (0.53 to 1.49)
	Modified TOAST	759	0.11 (0.06 to 0.19)	0.12 (0.07 to 0.22)
Previous TIA	Primary	1692	0.86 (0.65 to 1.14)	0.94 (0.70 to 1.27)
	All strokes included	2013	0.77 (0.60 to 1.00)	0.81 (0.62 to 1.06)
	POCI included	2132	0.89 (0.68 to 1.16)	0.95 (0.72 to 1.25)
	Cardioembolic excluded	1408	0.89 (0.66 to 1.20)	0.98 (0.71 to 1.34)
	Modified TOAST	759	0.68 (0.44 to 1.05)	0.71 (0.44 to 1.14)
Smoking	Primary	1692	1.30 (1.06 to 1.59)	1.16 (0.92 to 1.46)
	All strokes included	2013	1.37 (1.14 to 1.65)	1.20 (0.97 to 1.48)
	POCI included	2132	1.41 (1.16 to 1.70)	1.31 (1.06 to 1.62)
	Cardioembolic excluded	1408	1.09 (0.88 to 1.49)	1.12 (0.88 to 1.43)
	Modified TOAST	759	0.67 (0.49 to 0.93)	0.61 (0.41 to 0.88)
Alcohol excess	Primary	1692	1.09 (0.83 to 1.44)	0.79 (0.58 to 1.07)
	All strokes included	2013	1.05 (0.82 to 1.36)	0.74 (0.56 to 0.98)
	POCI included	2132	1.00 (0.77 to 1.29)	0.75 (0.57 to 1.00)
	Cardioembolic excluded	1408	1.11 (0.83 to 1.49)	0.84 (0.61 to 1.15)
	Modified TOAST	759	1.25 (0.79 to 1.97)	1.25 (0.74 to 2.11)

*Lacunar versus non-lacunar ischaemic stroke patients are compared in all analyses other than that of TOAST subtypes, where I compared patients with small versus large vessel disease (hence the fewer number of patients included in this latter analysis)
†Adjusted for age, sex, and all other risk factors included in the analysis
‡Cardioembolic source and ipsilateral carotid stenosis were included in modified TOAST definitions, so these variables were not analysed
POCI = posterior circulation ischaemic stroke; ICA = internal carotid artery; TIA = transient ischaemic attack; OR = odds ratio; CI = confidence interval

Table 7.4 Aetiological classification of ischaemic stroke subtypes according to clinical and imaging-based classification

		Aetiological classification according to Modified TOAST classification*						
Study	Clinical and imaging classification	Small vessel disease	Large vessel disease	Cardioembolic	Multiple aetiologies	Undetermined (complete investigation)	Undetermined (incomplete investigation)	Total
ESS	Lacunar	222 (78)	0 (0)	0 (0)	44 (15)	0 (0)	19 (7)	285 (100)
	Non-lacunar	0 (0)	79 (14)	120 (22)	15 (3)	279 (50)	60 (11)	553 (100)
	Total	222 (26)	79 (9)	120 (14)	59 (7)	279 (33)	79 (9)	838 (100)
LSR	Lacunar	350 (62)	0 (0)	0 (0)	50 (9)	0 (0)	165 (29)	565 (100)
	Non-lacunar	0 (0)	134 (14)	99 (10)	16 (2)	359 (38)	337 (36)	945 (100)
	Total	350 (23)	134 (9)	99 (7)	66 (4)	359 (24)	502 (33)	1510 (100)
ESS + LSR	Lacunar	572 (67)	0 (0)	0 (0)	94 (11)	0 (0)	184 (22)	850 (100)
	Non-lacunar	0 (0)	213 (14)	219 (9)	31 (2)	638 (43)	397 (27)	1498 (100)
	Total	572 (24)	213 (9)	219 (9)	125 (5)	638 (27)	581 (25)	2348 (100)

*Patients with an uncertain ischaemic stroke syndrome or an unusual cause of stroke such as arterial dissection have already been removed
ESS = Edinburgh Stroke Study; LSR = Lothian Stroke Register

7.4.4 Misclassification of ischaemic stroke subtypes

In the primary analysis population, 1806 patients had a visible relevant infarct on their scan, and 343 of these (19%) were allocated to a different comparison group than would have been the case based on their clinical syndrome alone. Applying the proportion misclassified (343 / 1806 [19%]) to the 1039 patients with no visible relevant infarct on their brain scan gave 197 patients who remained potentially misclassified. Therefore 197 / 2845 (7%) patients may have been misclassified in the whole primary analysis population. The proportion of patients misclassified was similar in each comparison group. When I repeated the primary analyses including only patients with a visible relevant infarct on brain imaging, I found very similar results to the primary analysis.

7.4.5 Updated meta-analysis

In my previous systematic review and meta-analysis, I identified 10 published studies that had used a clinical syndrome and imaging-based method of classifying ischaemic stroke subtypes that was independent of the patient's risk factors (Boiten *et al*. 1991; Hajat *et al*. 2001; Lodder *et al*. 1990; Mead *et al*. 1999b; Norrving & Cronqvist 1989; Sacco *et a*l. 2006; Somay *et al*. 2006; Tegeler *et al*. 1991; Toni *et al*. 1995), and three studies that relied on clinical syndrome, not modified by brain imaging (Lindgren *et al*. 1994b; Mead *et al*. 1998; Pittock *et al*. 2003). One study overlaps with the Lund register in my pooled individual patient data analysis and was therefore excluded from my updated meta-analysis (Lindgren *et al*. 1994b). Although this overlapping study previously reported results based on ischaemic stroke subtypes having been categorised using a clinical syndrome (not modified by brain imaging findings) classification method, it should be remembered that in the

Lund register included in my pooled individual patient data analysis the clinical symptoms and the site and size of any visible relevant infarcts on brain imaging was taken into account when we assigned the subtype classification.

Figure 7.5 shows, for each risk factor, the ORs for lacunar versus non-lacunar ischaemic stroke from my previous meta-analysis, from my unadjusted primary analysis of the collaborative individual patient dataset (including data from all five stroke registers), and from my updated meta-analysis incorporating the collaborative data. These three estimates were generally similar for all risk factors. The most consistent findings were a lower frequency among patients with lacunar ischaemic stroke of ischaemic heart disease (updated meta-analysis OR: 0.76, 95% CI 0.68 to 0.85), cardioembolic source (OR: 0.40, 95% CI 0.35 to 0.46), and carotid stenosis (OR for ipsilateral stenosis: 0.23, 95% CI 0.19 to 0.29; and for contralateral stenosis: 0.29, 95% CI 0.21 to 0.41); and no difference in the prevalence of diabetes or prior TIA. The updated meta-analysis showed a slight excess of hypertension among patients with lacunar ischaemic stroke (OR 1.12, 95% CI 1.02 to 1.24). It also suggested that smoking and excess alcohol consumption were more common in lacunar ischaemic stroke, but these results may be subject to residual confounding since they were not significant in fully adjusted analyses of the data from the two Edinburgh stroke registers. There was moderate heterogeneity between studies in my updated meta-analysis (due to variation between the results of published studies and not the collaborative registers) for each of ischaemic heart disease, cardioembolic source, ipsilateral stenosis, previous TIA and smoking.

Figure 7.5 Unadjusted ORs in the previous review, the individual patient data analysis, and the updated meta-analysis

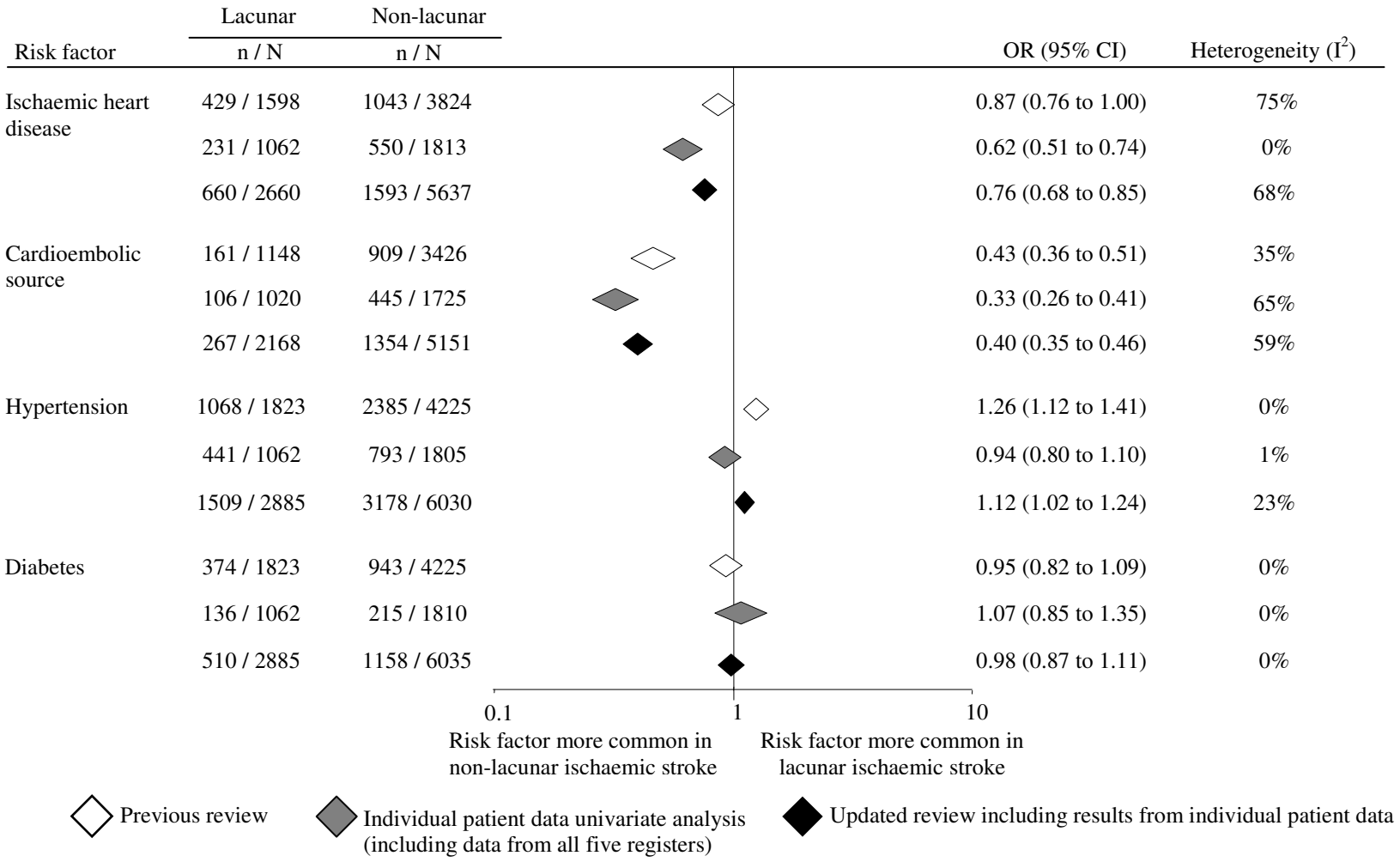
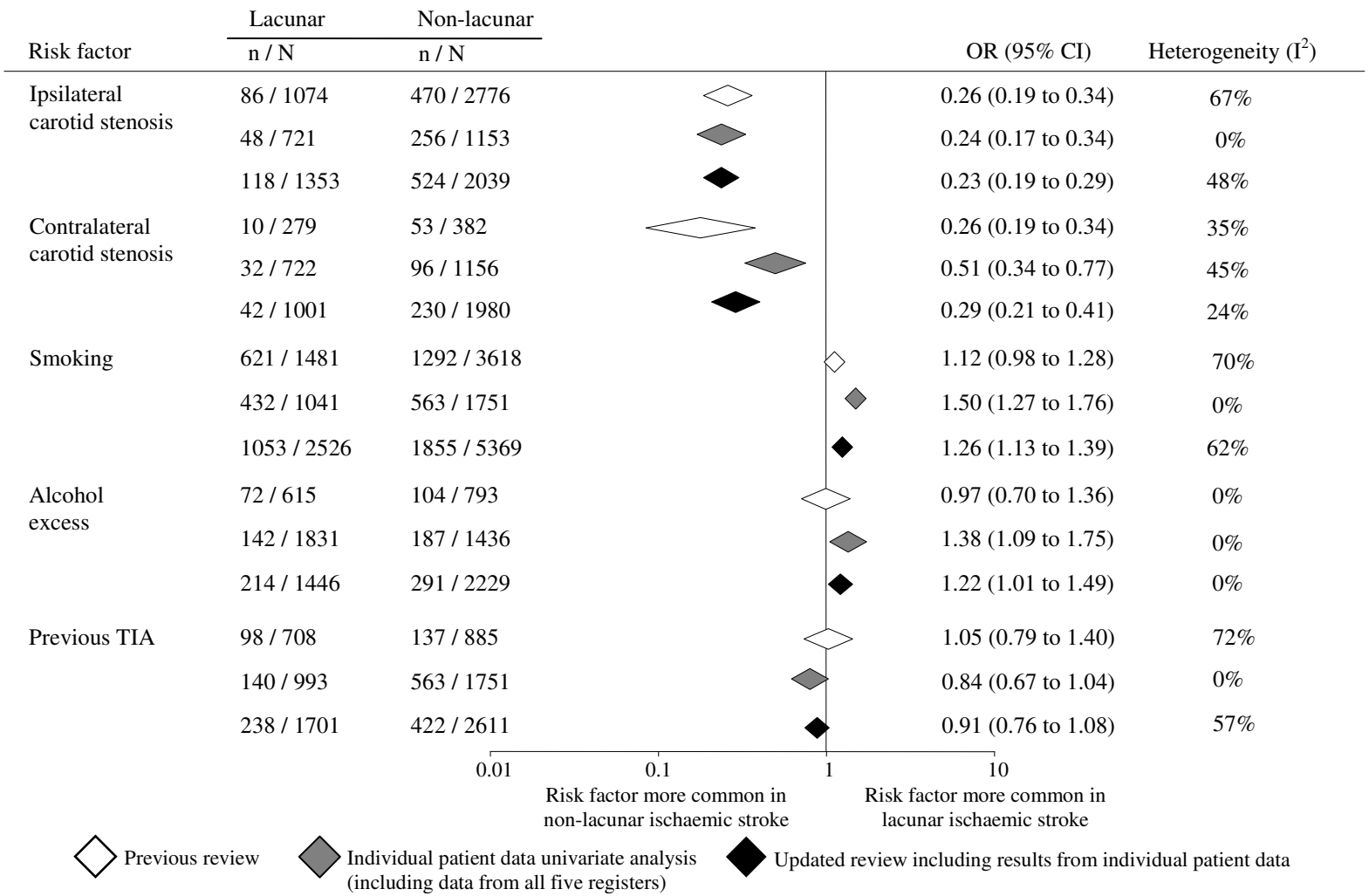


Figure 7.5 continued



7.5 Discussion

Analyses based on this large collaborative individual patient dataset revealed important differences in the risk factor profiles among patients with lacunar as compared with non-lacunar ischaemic stroke. There was a striking similarity between unadjusted and adjusted analyses of data from the Edinburgh stroke registers (which contributed 82% of the patients included in the entire collaborative dataset) and demonstrable robustness to a series of sensitivity analyses for most risk factors, providing methodological justification for the updated meta-analysis of unadjusted results from published studies. The individual patient data results were largely confirmed by the updated meta-analysis, and the overall evidence supports the notion of a distinct non-atherosclerotic arteriopathy causing many - perhaps most - lacunar ischaemic strokes.

Presence of a cardioembolic source and carotid artery stenosis were consistently less common in patients with lacunar than with non-lacunar ischaemic stroke, confirming that emboli from the heart or proximal arteries are much less likely to cause lacunar ischaemic stroke. My new clearly established finding that a history of ischaemic heart disease, a marker of systemic atherosclerosis, is less common in lacunar than non-lacunar patients provides further support for a distinct non-atherosclerotic lacunar arteriopathy. The results of my previous systematic review and meta-analysis where I included data from only those studies free from classification bias indicated that there was no difference in the frequency of diabetes. This finding has been confirmed and strengthened by these new - and now more robust - results. The results of my systematic review indicated that there may be a marginal excess of hypertension among lacunar as compared with non-lacunar patients when only

studies free from classification bias are analysed. However, in my individual patient data analysis hypertension is clearly equally common in patients with lacunar and non-lacunar ischaemic stroke. I also found no convincing, consistent differences in the frequency of each of previous TIA, smoking, or excess alcohol between lacunar and non-lacunar ischaemic stroke subtypes.

7.5.1 Strengths

There are considerable strengths to my collaborative individual patient data analyses and their inclusion in my updated meta-analyses. First, these analyses benefited from the methodological similarities between the included registers; the large numbers of patients, allowing more reliable detection of moderate differences in risk factor frequencies; and the opportunity to adjust for potential confounding factors. Second, their inclusion in the updated meta-analysis almost doubles the existing published data from studies using risk-factor free ischaemic stroke subtype classification methods on hypertension and diabetes, and more than doubles the existing data for many other risk factors analysed. Third, although adjustment for potential confounders made little difference to the results for most risk factors, it did suggest that confounding by other risk factors might explain the results for smoking and alcohol excess. Thus in my updated meta-analysis, smoking, alcohol excess and contralateral carotid stenosis appeared to be more common in lacunar ischaemic stroke, but my individual patient data adjusted analyses suggest that this may be due to confounding (and in the case of contralateral carotid stenosis, almost certainly due to a strong correlation with ipsilateral stenosis). Fourth, a series of sensitivity analyses in which I varied the lacunar and non-lacunar comparison groups did not substantially alter the overall or register-specific results. This suggests that the

observed heterogeneity between studies for some risk factor-stroke subtype associations in my updated meta-analysis is due less to variability in the non-lacunar comparison group or the inclusion of recurrent strokes and more to differences in risk factor definitions, the populations of patients studied, or other unidentified study characteristics.

7.5.2 Limitations

Although three of the five registers included in my individual patient data analysis were community-based, the two phases of the Edinburgh hospital-based register contributed the majority of the data. There is evidence that the distribution of, and risk factors for, ischaemic stroke subtypes differ between hospitalised and non-hospitalised patients (Schulz & Rothwell 2003). However, the hospital-based register patients in the present study were recruited from both hospital admissions *and* outpatient clinics, making them more representative. Furthermore, although community-based studies should avoid spurious risk factor-stroke subtype associations arising from selection bias, accurate classification of pathological stroke types and subtypes requires early specialist clinical assessment, appropriately timed brain imaging and other investigations, which would essentially confine analyses from community-based stroke registers to those patients having some sort of hospital-based assessment.

Although a classification method based on the clinical syndrome and brain imaging findings is probably the least biased method of assigning ischaemic stroke subtypes when investigating risk factor-stroke subtype associations, any classification system will result in some misclassification of ischaemic stroke subtypes. On the basis of the clinical syndrome alone, around 10-20% of small cortical ischaemic strokes tend

to be misclassified as lacunar and vice versa (Mead *et al*. 1999a), and in my collaborative individual patient dataset, I estimated that misclassification may have occurred in up to about 7% of the total number of patients included in our primary analysis. The effects are difficult to predict, but since the proportion of misclassified patients in the two compared groups of patients was similar, this would probably have caused a dilution of any true associations between risk factors and ischaemic stroke subtype. However, it seems unlikely that a strong association between, for example, hypertension and lacunar as compared with non-lacunar ischaemic stroke would be completely obscured by this, and it is reassuring that my analyses confined to patients with a visible relevant infarct on brain imaging produced similar results to the primary analysis, with the OR estimates in the same directions but with less precision due to inclusion of fewer patients.

It is also important to consider the potential for imprecise measurement and misclassification of the risk factors themselves. Ideally, data for risk factor comparisons between ischaemic stroke subtypes would come from large, population-based, prospective studies with detailed collection of risk factors at baseline; repeat risk factor measurements over time in subsets of subjects to permit adjustment for regression dilution bias; and rigorous follow-up over many years with careful subtyping of stroke outcomes, accruing in sufficient numbers for adequately powered comparisons between ischaemic subtypes. However, in practice, while analyses of pooled data from prospective studies have been highly informative about the nature of the relationship between several risk factors (such as blood pressure and blood cholesterol) and stroke in general, and – to some extent – the main pathological types of ischaemic and haemorrhagic stroke, the level of detail required for adequate

distinction between ischaemic stroke subtypes has rarely been available in prospective studies to date (Prospective Studies Collaboration 2007; Prospective Studies Collaboration 2002; Asia Pacific Cohort Studies Collaboration 2003). There are data from two small prospective studies, including about 300 (Tanizaki *et al*. 2000) and 500 (Ohira *et al*. 2006) stroke outcome events each, but they used potentially biased risk factor-dependent or imaging-based methods for classifying subtypes of ischaemic stroke. All the studies that I analysed used prospective methods to identify and subtype patients with stroke (in a hospital or community-based setting), but ascertained exposure to risk factors retrospectively, and so necessarily crudely. Taking blood pressure as an example, a simple dichotomy into those with or without hypertension loses valuable information on the nature of the relationship with stroke risk over a range of usual blood pressure, and any dichotomy based on retrospective information will necessarily be imprecise, whether it is based on a measure of pre-stroke blood pressure, a history of receiving treatment for hypertension, or post-stroke blood pressure (which may of course be influenced by the stroke itself). Furthermore, a definition based on a history of treated hypertension will of course have failed to identify those patients with previously undiagnosed hypertension. I could not measure misclassification of risk factor status, and although its effect on my results is difficult to predict, it seems most likely to have occurred to a similar extent in both comparison groups, and so to have been non-differential and to have diluted estimates of association. The implication is that, although my analyses were based on large numbers of patients, I may have failed to detect some risk factor-ischaemic stroke subtype associations, but there are simply not yet the robust prospective data to check whether this is the case.

I was unable to assess the relationship between raised cholesterol and lacunar versus non-lacunar ischaemic stroke in my dataset, since data on pre-stroke cholesterol levels were unavailable. As demonstrated in my systematic review and in a recent study (Amarenco *et al*. 2006), the current evidence suggests no definite association between cholesterol level and ischaemic stroke subtype.

7.5.3 Comparisons with other studies

In an earlier meta-analysis of four population-based studies, risk factor-stroke subtype associations were broadly similar to those from my individual patient data analyses, but ischaemic heart disease was not assessed (Schulz & Rothwell 2003). This meta-analysis found hypertension to be more frequent in lacunar as compared with non-lacunar ischaemic stroke, but this result could be attributed to a single large study that used strict application of the TOAST criteria with the reliance on risk factors to define subtypes and so potential for bias in addressing risk factor-stroke subtype associations.

In a recently published study that compared risk factor prevalence in stroke patients with presumed small vessel versus large vessel disease, hypertension appeared much more common in patients with small vessel disease (Khan *et al*. 2007). However, there are a number of important differences between this study and the studies included in my individual patient data analysis. First, the comparison groups in this study were not strictly consecutive and contemporaneous, with some of the patients included in the small vessel disease group recruited from centres different from those which recruited the large vessel disease group. Second, this study included post-stroke raised blood pressure in the definition of hypertension, whereas in the studies included in my individual patient data analysis hypertension was defined as a history

of treated hypertension prior to stroke onset. Third, and perhaps because of the differences in definitions, the proportion of patients classed as having hypertension was markedly higher in both the lacunar and non-lacunar comparison groups than in the studies included in our individual patient analysis. This high prevalence of hypertension inevitably leads to a more extreme OR than if the prevalence had been slightly lower in both groups, and this should be remembered when the OR is interpreted as a risk ratio. And finally, the method of classifying ischaemic stroke subtypes was different, with the authors using a modified TOAST classification to assign ischaemic stroke subtypes, excluding hypertension and diabetes from the definitions, but taking into account cardiac sources of emboli and degree of carotid stenosis. Interestingly, however, when I applied my own, similar, modified TOAST algorithm to the patients in our study and compared risk factor prevalence in those with small versus large vessel disease I obtained almost identical results to my primary analysis.

7.5.4 Conclusion

I confirmed in a large methodologically robust individual patient dataset, and in an updated meta-analysis including both this individual patient data and data from published studies free from classification bias, that a cardioembolic source and severe carotid stenosis are infrequently found in patients with lacunar ischaemic stroke and are much less prevalent than in patients with non-lacunar ischaemic stroke. This suggests that emboli from the heart or proximal arteries are likely to be the cause of only a minority of lacunar ischaemic strokes. Furthermore, my newly clearly established finding that the prevalence of previous ischaemic heart disease is also lower in patients with lacunar compared with non-lacunar ischaemic strokes,

provides further evidence against *in situ* atherosclerosis underlying most lacunar strokes.

In my individual patient analyses, hypertension and diabetes were consistently equally common in lacunar and non-lacunar ischaemic stroke, providing evidence against the still widely held belief that these risk factors are more prevalent in lacunar ischaemic stroke. When I combined the unadjusted individual data with data from published studies that used similar methods of classifying ischaemic stroke subtypes, there remained a suggestion that hypertension may be only marginally more common in patients with lacunar ischaemic stroke. The epidemiological evidence does not therefore support the view that hypertension is substantially more common in patients with lacunar ischaemic stroke.

Chapter 8. Do differences between ischaemic stroke subtypes in recurrent stroke and myocardial infarction support a distinct lacunar arteriopathy?: analysis of Edinburgh Stroke Study data

8.1 Aim

In this penultimate chapter, I report the results of my analyses where I addressed the final objective of my thesis, which was to compare risks of myocardial infarction and recurrent stroke, and recurrent stroke subtype patterns between ischaemic stroke subtypes, in patients followed up in the Edinburgh Stroke Study.

8.2 Introduction

Differences in the risk and patterns of vascular outcomes between lacunar and non-lacunar ischaemic stroke may reflect fundamentally different underlying pathologies. In the previous chapter, I demonstrated that patients with lacunar ischaemic stroke have a lower frequency of carotid stenosis and cardioembolic source than those with non-lacunar ischaemic stroke - suggesting that most lacunar ischaemic stroke is not caused by thromboemboli - and a lower frequency of prior ischaemic heart disease (a marker of systemic atherothrombosis), providing indirect evidence for an arterial pathology that is distinct from large artery atherothrombotic disease. If lacunar stroke is indeed mainly caused by a distinct non-atherothrombotic arterial pathology, then we would also expect a lower early recurrent stroke rate after lacunar compared with non-lacunar ischaemic stroke (because of a lower frequency of active sources of emboli); a tendency for recurrent stroke subtypes to breed true; and a lower risk of MI among patients with lacunar compared with non-lacunar ischaemic stroke. From

my systematic review and meta-analysis of published data, I found that, although existing studies have suggested a lower early recurrence rate among patients with lacunar ischaemic stroke and a tendency for recurrent stroke subtypes to breed true, the reliability of the results was limited by small numbers of patients, and variable, sometimes biased definitions of recurrent strokes. Also, brain imaging rates were low among patients following their recurrent stroke with no reports of the use of diffusion weighted magnetic resonance imaging (DW MRI), which is particularly helpful in differentiating new from old lesions, especially when they are small or when patients present late (Keir *et al*. 2004). Several cohort studies have assessed the incidence of MI after ischaemic stroke, which is reported to be about 2% per year, but only one has reported the risk of MI in lacunar and non-lacunar ischaemic stroke patients separately, and it included only 6 MIs (Landi *et al*. 1992). In the ESS, we aimed to address and overcome many of the methodological shortcomings of these previous studies.

8.3 Methods

I described the recruitment of patients, collection of baseline data, method of follow-up and ascertainment of outcome events in chapter 5, and will therefore reiterate only the salient methods here before describing the statistical analyses.

8.3.1 Study population

In my analyses I included all patients with a clinically evident stroke demonstrated to be ischaemic by the absence of recent intracerebral haemorrhage on CT or MR brain imaging, and who had been included in the follow-up component of the ESS.

8.3.2 Baseline and recurrent stroke data collection

Briefly, similar data were collected for the index and subsequent recurrent stroke, including data on: clinical features of stroke; primary prevention treatment at stroke onset; risk factor history; results of clinical investigations including brain imaging findings; clinical stroke syndrome using the OCSP classification (Bamford *et al*. 1991); and final stroke subtype, based on clinical stroke syndrome modified by brain imaging findings to give a final classification of LACI, PACI, TACI, POCI or uncertain subtype.

8.3.3 Ascertainment and definition of outcome events

We followed patients for a minimum of one year and a maximum of four years, using multiple overlapping methods to ascertain death, recurrent stroke and MI. These methods included contact with GPs, patients, and the General Registry Office for Scotland, and, where necessary, review of hospital and GP medical records and autopsy reports.

We defined recurrent stroke using the same definition as for the index stroke, with the added criterion that there had to be a period of clinical stability for at least 24 hours between the index and recurrent stroke, and intercurrent illness, cerebral oedema and haemorrhagic transformation had to be excluded as potential causes of any neurological worsening. Where there were insufficient clinical details about a potential recurrent stroke, and no brain imaging was performed, we considered the event as a possible recurrent stroke only. Most patients with a suspected recurrent stroke were assessed as an inpatient or outpatient by a stroke specialist. For patients with a suspected MI, or those unable to attend a face-to-face clinical assessment for suspected recurrent stroke, we confirmed occurrence of the event by independent

review of all relevant medical records and results of investigations. Where possible, we obtained CT and/or advanced MR brain imaging with T2, gradient echo, fluid-attenuated inversion recovery and diffusion weighted (DW) imaging sequences in patients with a suspected recurrent stroke, and in particular performed DW MRI if CT revealed no visible relevant lesion.

We diagnosed definite MI where there was either: (1) autopsy evidence of acute MI, or (2) evidence of two of the following: symptoms of ischaemia (e.g. chest pain); enzyme changes indicative of MI (generally raised troponin); ECG changes suggestive of new ischaemia (new ST-T changes or left bundle branch block). We assigned a probable MI when the patient died suddenly and unexpectedly, without evidence of a non-cardiac cause and with no subsequent autopsy examination.

8.3.4 Statistical analyses

I performed statistical analyses using STATA version 8.0 (StataCorp 2003).

8.3.4.1 Descriptive analyses

In my primary analysis I compared baseline characteristics of patients with a first-ever-in-a-lifetime lacunar versus non-lacunar anterior circulation ischaemic stroke (i.e. patients with LACI versus PACI or TACI) using the χ^2 test for dichotomous variables, Student's t-test for normally distributed continuous variables, the Mann Whitney U-test for non-normally distributed continuous variables and the χ^2 test for trend for ordered categorical variables. I calculated the median length of follow-up as the median observation time (time from entry into study to date of death or date censored).

8.3.4.2 Assessment and quantification of follow-up completeness

I determined the proportion of patients included in the primary analysis (i.e. lacunar and non-lacunar patients) who were completely followed up by each method, calculating the proportion of patients:

- who had died and for whom we had received cause of death information from the GRO;
- whose GP was contacted to inform them of their inclusion in the study;
- whose GP completed postal forms in the GP survey at the end of the follow-up period;
- who returned all postal questionnaires.

To determine a minimum estimate of completeness of follow-up, I quantified completeness of follow-up using a method modified from Clark *et al*. 2002. For each patient, I determined the percentage of completeness of follow-up by determining the ratio of the observed follow-up time to the potential follow-up time:

$$\% \text{ completeness} = \left(\frac{\text{observed follow-up time}}{\text{potential follow-up time}} \right) * 100$$

I then applied the following equation to obtain an overall follow-up completeness index (C) for all patients (Clark *et al*. 2002):

$$C = 100 \sum_{i=1}^{n} t_i / \sum_{i=1}^{n} t_i^*$$

t_i = observed, possibly censored, survival time for the ith participant
t_i^* = ith participants follow-up time; n = number of participants

For the purposes of this analysis, I considered recurrent stroke as the primary outcome of interest. I defined the potential follow-up time as the time from entry of the patient into follow-up to the end point of the study or the date patients were censored (the date of recurrent stroke if it occurred, or date of death). I defined observed follow-up as the time from entry of the patient into follow-up to the date patients were censored (date of recurrent stroke if it occurred, or date of death), or the date of last contact with each patient. I defined last contact date as: the end point of the study if a patient had returned all postal questionnaires; the date the last postal questionnaire was completed if subsequent questionnaires were not returned; the date of clinical assessment of baseline stroke if no questionnaires were returned and there was no further direct contact between one of our clinical stroke specialists and the patient, or the date that a patient was last reviewed by a stroke specialist if there was further direct contact. To identify any difference in completeness of follow-up between the comparison groups included in my primary analysis, I compared the proportion of patients with 100% complete follow-up among patients with lacunar and non-lacunar ischaemic stroke using the χ^2 test. Since completeness of follow-up is likely to be affected by the number of outcome events I also compared completeness of follow-up between my comparison groups having excluded patients who experienced a recurrent stroke or died.

8.3.4.3 Survival analysis

I used survival analysis techniques to determine the survival patterns for each of death, recurrent stroke and MI among patients with anterior circulation lacunar and non-lacunar ischaemic stroke, censoring patients at time of their non-fatal event or death, or at the end of the follow-up period, and compared reverse Kaplan Meier

survival (i.e. cumulative incidence) curves using the log-rank test. I used Cox regression to obtain unadjusted and age and sex-adjusted hazard ratios for death and for recurrent stroke (lacunar versus non-lacunar) for the entire follow-up period and for pre-defined time periods: 0-1 year and 1-4 years; 0-1 month and 1 month-4 years; and (for recurrence only) 0-1 week and 1 week-4 years. I was unable to adjust recurrent stroke hazard ratios at one month and one week for age and sex due to low numbers of recurrent events in the early period. I assessed for violation of the proportional hazards assumption by plotting log cumulative hazard against time for dichotomous variables, and by plotting Schoenfeld residuals for continuous variables. The proportional hazards assumption was not violated for each of stroke subtype, gender and age in the analyses of death and recurrent stroke (Appendix 12a and 12b). I obtained unadjusted rate ratios for MI, comparing patients with lacunar versus non-lacunar ischaemic stroke. It was not possible to adjust the MI risk comparison for confounding factors using multivariable survival analysis techniques because the proportional hazards assumption was violated, with the survival curves for lacunar and non-lacunar patients overlapping multiple times (Appendix 12c). As an alternative method of controlling for prior IHD, which is likely to be the most important confounding factor in this case, I repeated the univariate analysis but excluded patients with previous IHD (see footnotes to Table 8.1 for definition).

8.3.4.4 Sensitivity analyses

To control for the effect of stroke severity on the rates of death in lacunar compared with non-lacunar ischaemic stroke, I performed a sensitivity analysis where I compared patients with lacunar versus mild cortical (PACI) stroke.

To test the robustness of the primary analysis results and to determine whether the choice of comparison groups has an effect on the results I repeated the above analyses of rates of recurrent stroke and MI in a series of pre-defined sensitivity analyses, altering the comparison group each time:

(1) I compared risks of MI and recurrent stroke in patients with lacunar stroke compared with mild cortical stroke (i.e. PACI) to compare vascular outcome rates in patients with similar stroke severity

(2) I applied my modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) algorithm (as described in the previous chapter; Figure 7.1) to assign an aetiological stroke classification to each patient and compared patients with presumed small vessel versus large vessel disease (thus excluding patients with a presumed cardioembolic stroke or stroke of an undetermined cause)

(3) I repeated the MI analyses but included patients with definite MI only

8.3.5 Analysis of recurrent stroke subtype patterns

I analysed recurrent stroke subtype patterns by calculating unadjusted odds ratios for a lacunar or a non-lacunar recurrence following a lacunar versus non-lacunar stroke at baseline. I used logistic regression analysis to adjust these odds ratios for potential confounding by age, sex and antiplatelet or anticoagulant therapy at onset of recurrent stroke. I adjusted for treatment because this may differ according to baseline stroke subtype, and may also influence the type of ischaemic recurrent stroke (e.g. warfarin treatment for AF may be more commonly used in patients with non-lacunar ischaemic stroke, and may particularly reduce the risk of cardioembolic ischaemic stroke).

Inclusion of recurrences that occurred during the early period might bias analyses of recurrent stroke subtype patterns since these early recurrences may be more likely to be of the same subtype as the index stroke as a result of further thrombus or emboli from unstable atherosclerotic plaque in carotid arteries, for example, and not necessarily because stroke subtypes breed true to type in the longer term. I therefore performed a sensitivity analysis where I repeated the above analyses but excluded all recurrent events occurring within the first 30 days post-stroke.

8.3.6 Updated meta-analysis of recurrent stroke subtype patterns

I updated my meta-analysis of data from studies reporting patterns of recurrent stroke subtypes among patients with lacunar versus non-lacunar ischaemic stroke, to include data from the ESS. I determined fixed-effect study-specific and summary odds ratios of having a lacunar recurrence (for lacunar versus non-lacunar ischaemic stroke at baseline) and a non-lacunar recurrence (for lacunar versus non-lacunar ischaemic stroke at baseline), with their accompanying 95% confidence intervals using Cochrane Review Manager. I assessed heterogeneity between studies using the I^2 statistic (Higgins & Thompson 2002).

8.3.7 Estimation of ischaemic stroke subtype misclassification

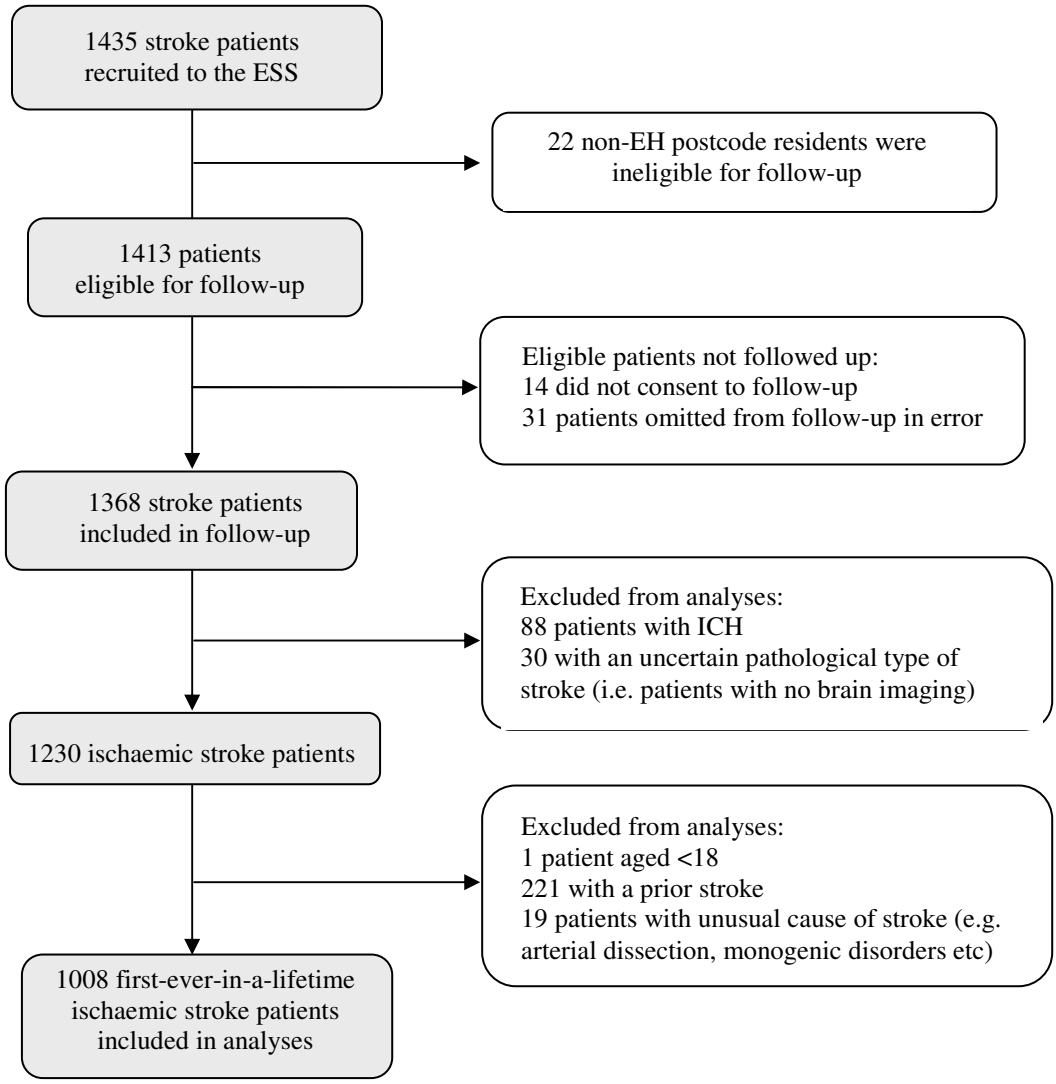
I estimated the extent of misclassification of ischaemic stroke subtypes by calculating the proportion of patients with a visible relevant infarct on their brain scan whose final classification placed them in a different comparison group (i.e. lacunar or non-lacunar) from their classification based on the clinical syndrome alone. I then applied this proportion to the patients who had no visible relevant infarct on brain imaging to estimate the extent of residual misclassification among both baseline and recurrent ischaemic stroke subtypes.

8.4 Results

8.4.1 Baseline characteristics of patients

Of 1413 stroke patients recruited into the ESS and eligible for inclusion in follow-up, 1368 (97%) were followed up (Figure 8.1). As presented previously, just 14 patients (1%) who gave their consent for their data to be collected for research purposes did not consent to the follow-up component of the study.

Figure 8.1 Flow diagram of Edinburgh Stroke Patients included in analyses



Of the 1368 patients followed up, 1230 had had an ischaemic stroke. After excluding one patient aged less than 18, 19 patients whose stroke was known to have been due to an unusual cause, and patients with a previous history of a symptomatic stroke, this left 1008 patients who had had a first-ever-in-a-lifetime stroke, all of whom underwent brain imaging. Of these, 809 patients had an anterior circulation ischaemic stroke (282 were lacunar and 527 were non-lacunar) and were followed up for a median of 2.4 (interquartile range 1.7 to 3.2) years, giving a total follow-up time of 1726 person-years.

Patients with lacunar ischaemic stroke were slightly younger than those with non-lacunar ischaemic stroke (mean 69 vs 73 years; $p < 0.001$) and there were more men in the lacunar compared with the non-lacunar group (60% vs 47%; $p = 0.001$; Table 8.1). The delay from onset of stroke symptoms to clinical assessment was slightly longer for patients with lacunar than non-lacunar ischaemic stroke (median 12 vs 7 days; $p < 0.001$), with the delay to assessment reflecting the inclusion of patients who were assessed in outpatient clinics. More patients with lacunar than non-lacunar ischaemic stroke were assessed in outpatients, hence the slightly longer time to clinical assessment in the former group.

Among patients who had CT brain imaging only (and not MR brain imaging), a greater proportion of lacunar than non-lacunar cases was scanned more than 7 days after symptom onset (51% vs 41%; $p = 0.02$), but few patients in both groups were scanned at more than one month post-stroke (12% vs 9%; $p = 0.22$). More than one quarter of lacunar patients and about one fifth of non-lacunar patients had MRI at baseline, with no significant difference in time between symptom onset and MR brain scan (Table 8.1).

Table 8.1 Baseline characteristics of lacunar and non-lacunar anterior circulation ischaemic stroke patients included in the primary analysis

Characteristic	All patients (809)	Anterior circulation		p value
		Lacunar (282)	Non-lacunar (527)	
Demographics				
Age (mean years ± SD)	72 (±12)	69 (±12)	73 (±12)	<0.001
Male (%)	418 (52)	168 (60)	250 (47)	0.001
Clinical risk factors				
Hypertension[*] (%)	414 (51)	135 / 282 (48)	279 / 527 (53)	0.17
Diabetes mellitus[†] (%)	91 (11)	38 / 282 (13)	53 / 527 (10)	0.14
Previous TIA (%)	141 (17)	47 / 282 (17)	94 / 525 (18)	0.53
Previous IHD[‡] (%)	203 (25)	56 / 282 (20)	147 / 527 (28)	0.01
Atrial fibrillation[¶] (%)	177 (22)	34 / 281 (12)	143 / 527 (27)	< 0.001
Ipsilateral carotid stenosis[#] (%)	106 (14)	13 / 271 (5)	93 / 479 (18)	< 0.001
Contralateral carotid stenosis[#] (%)	43 (5)	12 / 271 (4)	31 / 482 (6)	0.26
Clinical assessment				
Independent in ADL pre-stroke	766 (95)	274 / 282 (97)	492 / 525 (93)	<0.01
NIHSS (median [IQR])	1 (0-4)	1 (0-3)	2 (0-7)	< 0.001
Time to assessment (median days [IQR])	9 (2-20)	12 (4-22)	7 (1-19)	< 0.001
Brain imaging				
CT (%)	662 (81)	217 / 282 (78)	445 / 527 (84)	0.01
Median days from onset to CT (IQR)	4 (1-18)	7 (1-19)	3 (1-17)	0.001
Scanned > 7 days post-stroke (%)[**]	276 / 619 (45)	105 / 206 (51)	171 / 413 (41)	
Scanned > 30 days post-stroke (%)[**]	62 / 619 (10)	25 / 206 (12)	37 / 413 (9)	
MRI (%)	189 (23)	76 / 282 (27)	113 / 527 (21)	0.17
Median days from onset to MRI (IQR)	19 (4-35)	21 (14-22)	18 (1-38)	0.13

[*]History of treated hypertension
[†]previously diagnosed with or on medication for diabetes mellitus
[‡]history of myocardial infarction (including ECG evidence of silent myocardial infarction), angina or coronary revascularisation
[¶]history, or post-stroke electrocardiogram evidence, of paroxysmal or persistent atrial fibrillation
[#]severe carotid stenosis defined as ≥ 70% internal carotid artery stenosis (ECST criteria)
[**]including patients who had CT brain imaging only
TIA = transient ischaemic attack; IHD = ischaemic heart disease; ADL = activities of daily living; NIHSS = National Institute of Health Stroke Score; IQR = interquartile range; CT = computed tomography; MRI = magnetic resonance imaging

8.4.2 Completeness of follow-up

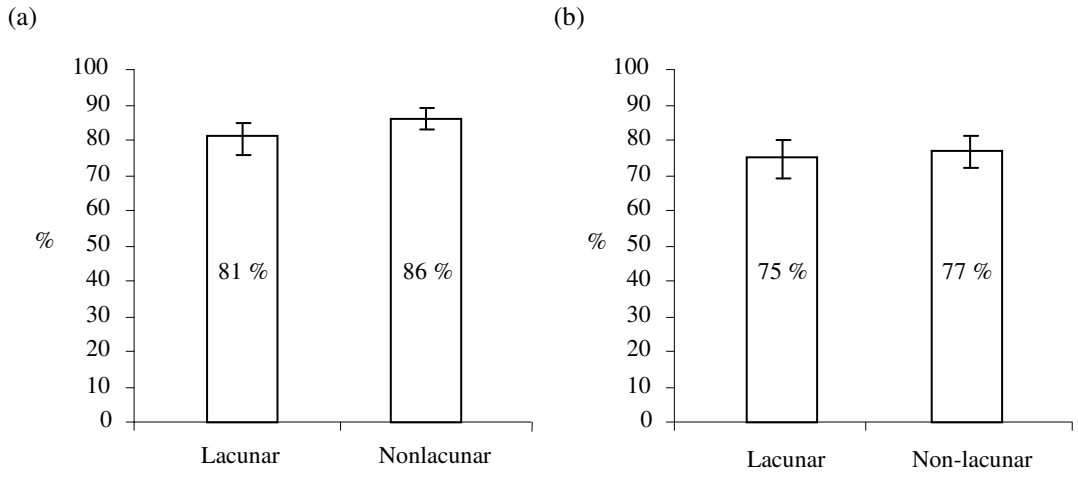
There were no patient withdrawals from the study, and no patient was entirely lost to follow-up. Five patients withdrew from the postal questionnaire follow-up aspect of the study, but were still followed up by other methods. The estimated completeness of each follow-up method is detailed in Table 8.2. It was not possible to determine whether contact cards were always given to patients or whether study stickers were always added to patients' notes. Patient response to postal questionnaires was good, with 72% returning all questionnaires sent to them and 88% returning at least the first (6-month) questionnaire.

Table 8.2 Completeness of follow-up

Follow-up method	Details	Completeness of follow-up method
General Registry Office for Scotland	All patients were flagged at the General Registry Office, to obtain notification and cause of death	Data on 1367 (100%) patients provided to the GRO for flagging purposes
		Cause of death data received from GRO for 338 / 356 (95%) patients known to have died
GP contact	Letters sent to GP when patient entered into the study, requesting that they inform us of further vascular events and/or death	Letters sent to GPs of all 1367 patients (100%)
	GP survey: at end of study, questionnaires sent to GPs of all living patients to enquire about the occurrence of further vascular events during the entire course of the study	Form returned by GP for 792 / 1014 patients (78% of living patients)
Contact cards	Patients were given a study contact card and asked to contact the study team if they had another stroke or an MI	Inestimable
Postal questionnaire	Patients still alive at 6 months, 1 year (and annually thereafter) were sent a postal questionnaire	882 / 1217 (72%) patients returned all questionnaires sent to them
ESS Stickers	Study stickers were placed on the front of hospital medical records and were provided to GPs to place on the front of primary care medical records	Inestimable

The completeness of follow-up - as measured by postal questionnaire response - was 84%. This is a minimum estimate of overall completeness of follow-up, because it does not take into account our other methods of follow-up which were not analysable by this method of estimating completeness. Slightly more patients with non-lacunar than lacunar ischaemic stroke had 100% complete follow-up (86% vs 81%, p = 0.05; Figure 8.2a). However, this is probably explained by the increased number of outcome events (and thus more patients with 100% follow-up) in the non-lacunar group, because when I excluded patients who had had a recurrent stroke or died, there was very little difference in the proportion of patients who were completely followed up (77% vs 75%, p = 0.51; Figure 8.2b).

Figure 8.2 Proportion of lacunar and non-lacunar patients with complete (100%) follow-up by postal questionnaire: (a) including all patients and (b) excluding patients who had had a recurrent stroke or died



8.4.3 Death

Among all 809 patients with anterior circulation ischaemic stroke, 191 (24%) died during follow-up. Of these, 127 (66%) were deaths due to a vascular cause. Specifically, deaths were due to stroke (77 [40%]); cardiac causes (35 [18%]), cancer (32 [17%]), chest infection (12 [6%]), chronic obstructive pulmonary disease (5 [3%]), ischaemic bowel (4 [2%]), other causes such as sepsis, liver failure, vascular dementia etc (21 [11%]), and unknown cause (5 [13%]).

Of the 191 deaths, 38 (13%) were among patients with lacunar ischaemic stroke and 153 (29%) were among patients with non-lacunar ischaemic stroke (Table 8.3). Death was due to a vascular cause in 19 of the 38 (50%) lacunar patients, and 108 of the 153 (71%) non-lacunar patients.

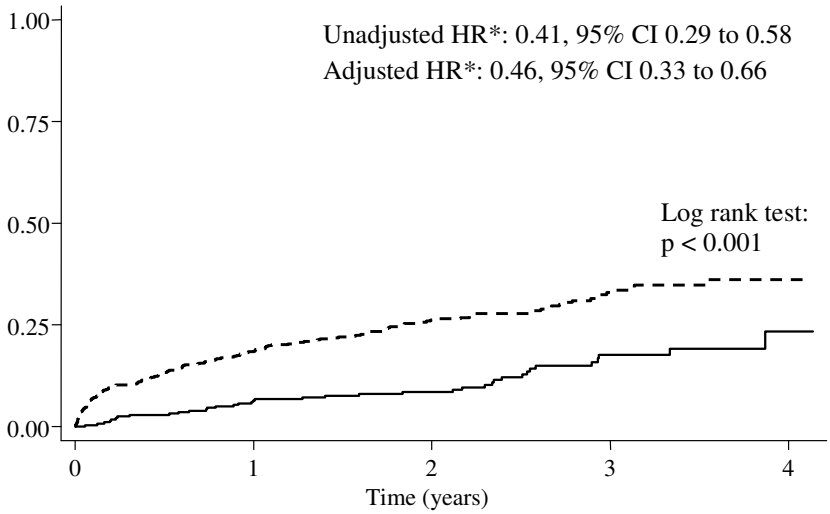
Table 8.3 Outcome events among lacunar and non-lacunar anterior circulation ischaemic stroke patients

		Ischaemic stroke subtype		
			Non-lacunar	
Outcome event	**All patients (809) n (%)**	**Lacunar (282) n (%)**	**All (527) n (%)**	**PACI (442) n (%)**
Death	191 (24)	38 (13)	153 (29)	101 (23)
Recurrent stroke	109 (13)	36 (13)	73 (14)	64 (14)
Myocardial infarction				
All	33 (4)	8 (3)	25 (5)	21 (5)
- Fatal	11 (1)	1 (0.4)	10 (2)	7 (2)
- Non-fatal	22 (3)	7 (2)	15 (3)	14 (3)

TACI = total anterior circulation infarction; PACI = partial anterior circulation infarction

Over the entire follow-up period, risk of death was significantly lower in the lacunar than in the non-lacunar ischaemic stroke group (unadjusted HR 0.41, 95% CI 0.29 to 0.58), as demonstrated in the reverse Kaplan Meier survival plot (Figure 8.3; log rank $p < 0.001$). After adjusting for age and sex the difference in risk of death attenuated only very slightly, with the rate of death in lacunar patients about 50% lower than in non-lacunar patients (adjusted HR 0.46, 95% CI 0.33 to 0.66). The difference in risk of death was most prominent during the early (one-month) post-stroke period (Figure 8.3 & Figure 8.4), although there was still a trend towards a lower risk of death among patients with lacunar compared with non-lacunar ischaemic stroke in the longer term, even after I accounted for stroke severity in a sensitivity analysis where I compared patients with lacunar versus mild cortical ischaemic stroke (PACI) (Figure 8.4).

Figure 8.3 Plot of cumulative probability of death, among lacunar and non-lacunar ischaemic stroke patients

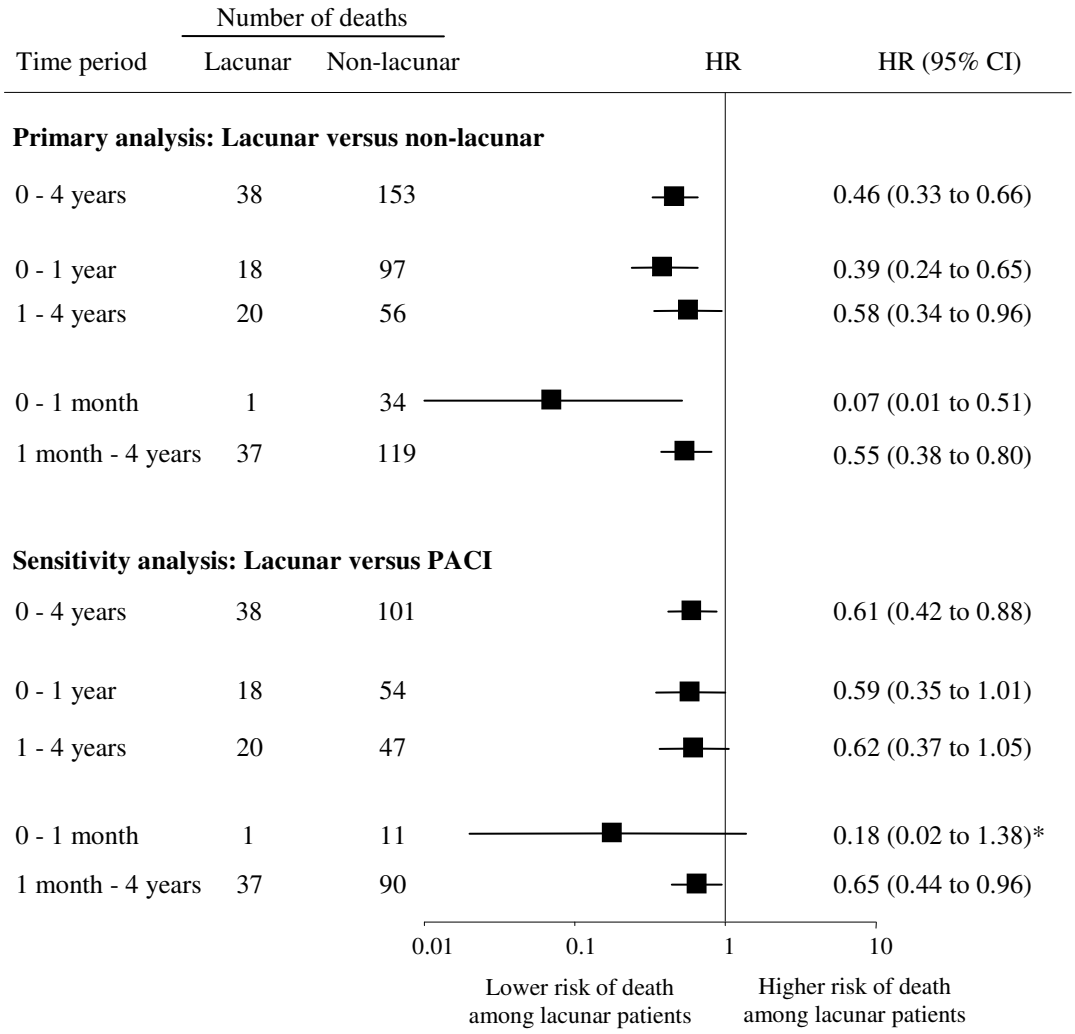


Number at risk

Lacunar (——)	282	264	168	86	5
Non-lacunar (- - -)	527	430	262	120	5

*Cox regression. HR = hazard ratio; CI = confidence interval

Figure 8.4 Age and sex-adjusted hazard ratios for death, for the entire follow-up period and for pre-defined time periods, in primary and sensitivity analyses



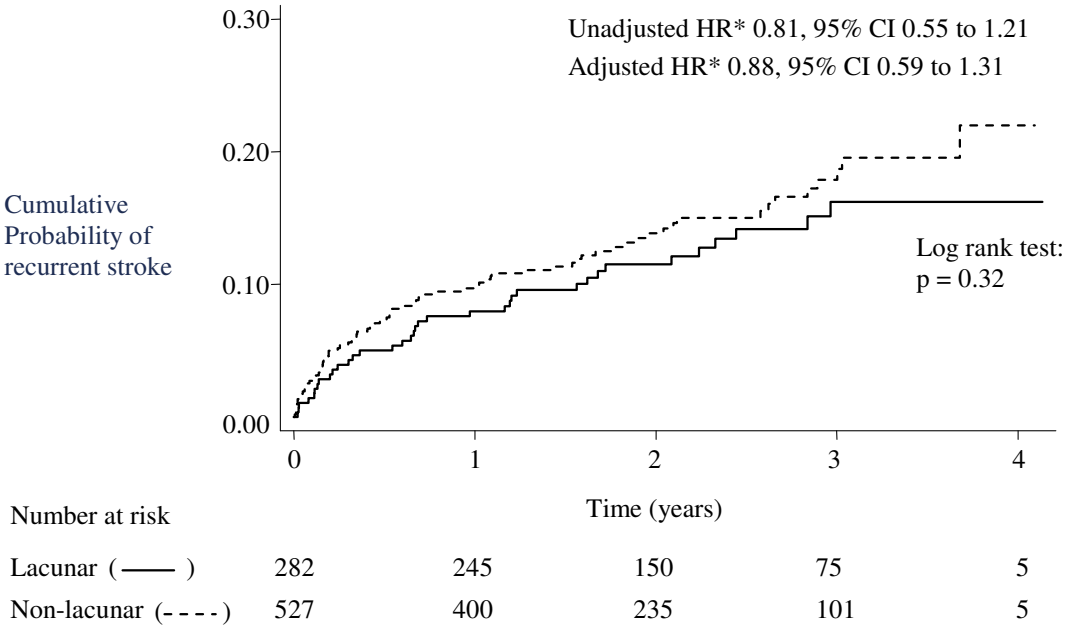
*unadjusted hazard ratio
HR = hazard ratio; CI = confidence interval; PACI = partial anterior circulation infarction

8.4.4 Recurrent stroke

Among patients included in the primary analysis, 109 (13%) had at least one recurrent stroke during follow up (Table 8.3). Thirty-six (13%) patients with a lacunar ischaemic stroke at baseline had a recurrent stroke and 73 (14%) patients

with a non-lacunar ischaemic stroke at baseline had a recurrent stroke (9 [11%] among patients with a TACI and 64 [14%] among patients with a PACI).

Figure 8.5 Plot of cumulative probability of recurrent stroke, among patients with lacunar and non-lacunar ischaemic stroke



*Cox regression
HR = hazard ratio; CI = confidence interval

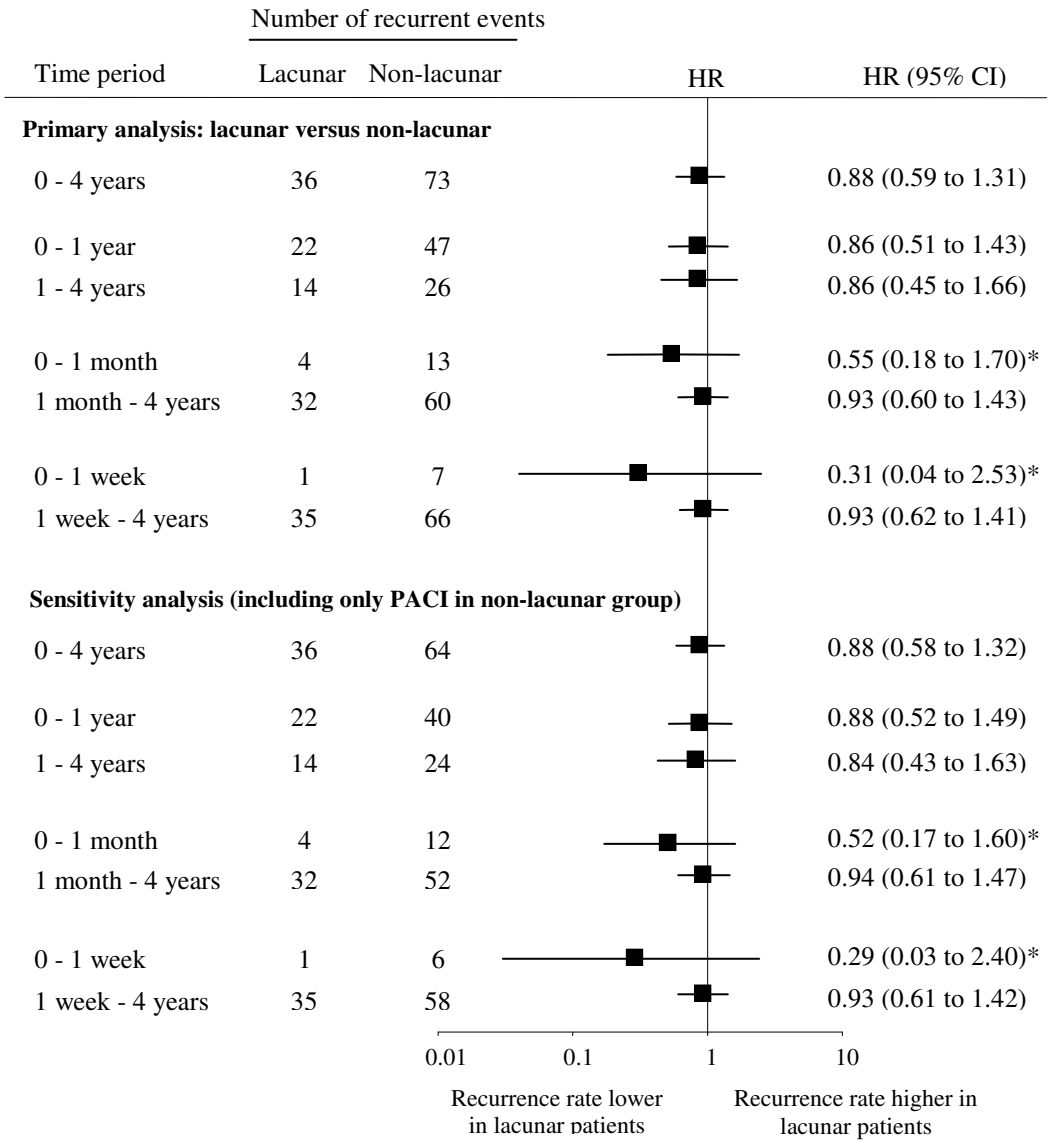
Over the entire follow-up period, there was no statistically significant difference in rate of recurrence between patients with lacunar versus non-lacunar ischaemic stroke (unadjusted HR 0.81, 95% CI 0.55 to 1.21), with the Kaplan Meier reverse survival plots very similar for both groups (log rank p value = 0.32; Figure 8.5). This lack of difference remained after adjusting for age and sex (adjusted HR 0.88, 95% CI 0.59 to 1.31). There was a non-significant trend towards a lower rate of recurrent stroke during the first month among patients with lacunar ischaemic stroke (unadjusted HR

0.55, 95% CI 0.18 to 1.70), with no evidence of any difference thereafter (Figure 8.6). This difference in recurrence rate was greater when I examined the very early (i.e. first week) period (unadjusted HR 0.31, 95% CI 0.04 to 2.53), but precision was limited by small numbers of early recurrences (at one week 1 patient in the lacunar group had a recurrence versus 7 in the non-lacunar group). However, due to the delay between onset and clinical assessment, we probably underestimated the early stroke recurrence risk, particularly among patients with non-lacunar stroke at baseline, and hence underestimated the extent of the reduced early recurrence risk among patients with lacunar as compared with non-lacunar stroke. After I excluded the first week post-stroke, there was no clear difference in the rate of recurrence thereafter (age and sex-adjusted HR 0.93, 95% CI 0.62 to 1.41; Figure 8.6).

The results of my sensitivity analyses were very similar to the results of my primary analysis. When I compared risk of recurrence in patients with lacunar versus mild cortical ischaemic stroke (i.e. PACI), I found very similar results to those in the primary analysis when I analysed the entire follow-up period (adjusted HR 0.88, 95% CI 0.58 to 1.32), the one month period (unadjusted HR 0.52, 95% CI 0.17 to 1.60), and the one week period (unadjusted HR 0.29, 95% CI 0.03 to 2.40), although again, low numbers of very early recurrences limited the precision of effect estimates in the acute period (Figure 8.6). When I compared risk of recurrence in patients with presumed small vessel versus large vessel disease, I found no significant difference in risk of recurrence during the entire follow-up period once I adjusted for confounding by age and sex (adjusted HR 0.56, 95% CI 0.30 to 1.05; p = 0.07), and no difference at one month, although numbers of outcome events (n = 5) were low once patients were classified according to presumed aetiological cause. There were

no very early recurrent strokes among patients with presumed small vessel disease, which prohibited analysis of the one-week period.

Figure 8.6 Age and sex-adjusted hazard ratios (lacunar versus non-lacunar ischaemic stroke) for recurrence risk during the entire follow-up period, and at specific time periods, in primary and sensitivity analyses

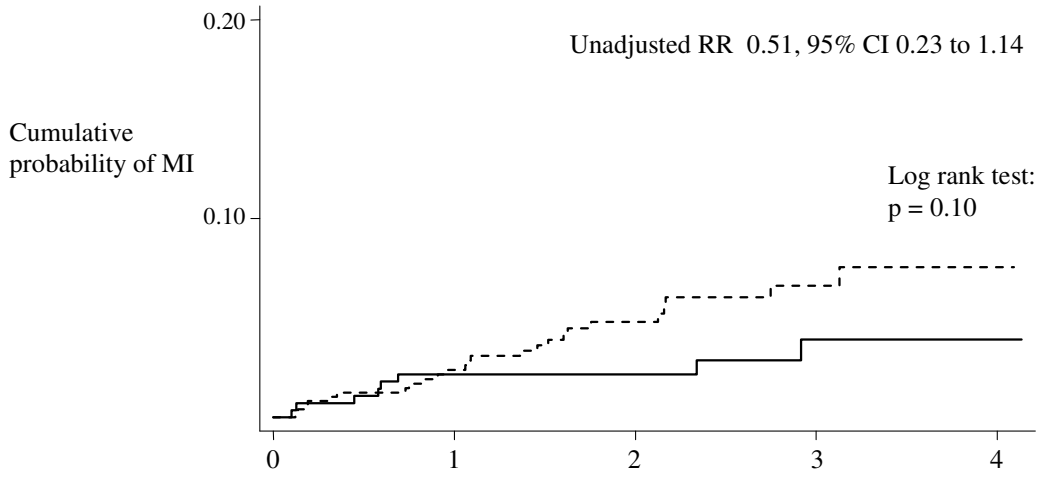


*Unadjusted for age and sex
HR = hazard ratio; CI = confidence interval; PACI = partial anterior circulation infarction

8.4.5 Myocardial infarction

Twenty-five (5%) patients with a non-lacunar ischaemic stroke at baseline subsequently had an MI compared with 8 (3%) patients with a lacunar ischaemic stroke at baseline (Table 8.3). Although the Kaplan Meier plot suggested a reduced risk of MI following lacunar compared with non-lacunar ischaemic stroke (Figure 8.7), this was not statistically significant (log rank p value = 0.10; rate ratio 0.51, 95% CI 0.23 to 1.14).

Figure 8.7 Plot of cumulative probability of MI, among patients with lacunar and non-lacunar ischaemic stroke



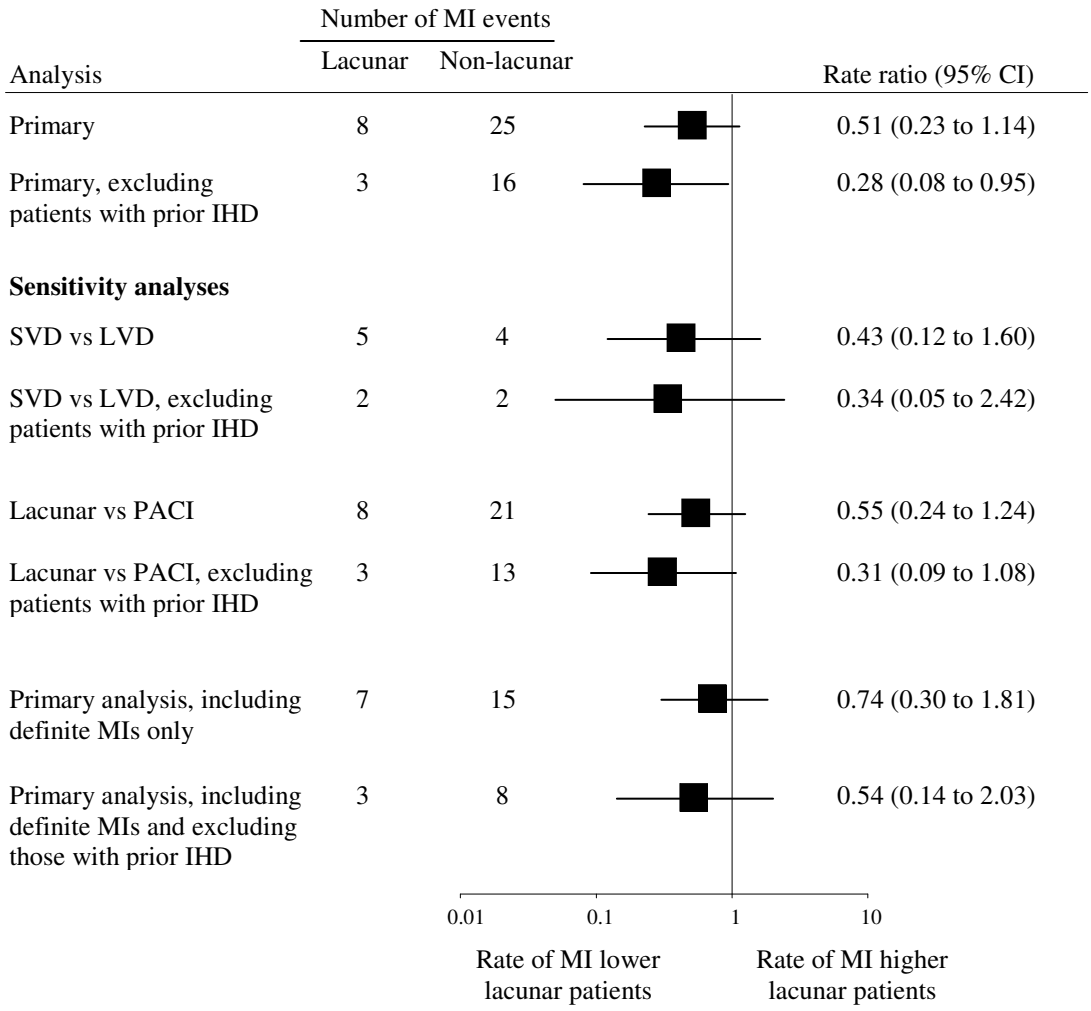
Number at risk					
Lacunar (——)	282	262	166	86	5
Non-lacunar (- - - -)	527	423	257	116	5

RR = rate ratio; CI = confidence interval; MI = myocardial infarction

When I limited my analysis to patients without a prior history of IHD, the association between lacunar stroke and a reduced rate of MI became more extreme, and reached statistical significance albeit with poor precision due to reduced numbers of patients (rate ratio 0.28, 95% CI 0.08 to 0.95). The results were essentially unchanged in my

sensitivity analyses, where I compared MI risk in patients with: small versus large vessel disease; lacunar stroke versus PACI; and where I included definite MIs only. Effect estimates became less precise however, due to inclusion of fewer patients (Figure 8.8).

Figure 8.8 Rate ratios of myocardial infarction, comparing lacunar with non-lacunar patients in the primary analysis, and varying the comparison groups in sensitivity analyses



MI = myocardial infarction; IHD = ischaemic heart disease; SVD = small vessel disease; LVD = large vessel disease; PACI = partial anterior circulation infarction

8.4.6 Recurrent stroke subtype patterns

Brain imaging was available to confirm the main pathological type of recurrent stroke (ischaemic or haemorrhagic) and to help with assigning an ischaemic subtype in 93% of patients with a recurrent stroke, and one patient had autopsy but no brain imaging. Of the patients with brain imaging, 64% had CT imaging and 54% had advanced MR imaging including diffusion weighted sequences (Table 8.4). We assigned a pathological subtype (TACI, PACI, LACI, POCI) in 97 of 98 cases of recurrent ischaemic stroke. Over three quarters of patients with recurrent ischaemic stroke had a visible relevant infarct on brain imaging (Table 8.5). Among patients with PACI and lacunar ischaemic stroke (between which there is the greatest degree of clinical subtype misclassification), three quarters and two thirds, respectively, had a visible relevant infarct on brain imaging.

Table 8.4 Brain imaging characteristics of patients with recurrent stroke following anterior circulation ischaemic stroke at baseline

Brain imaging	**All patients (N = 109)**	**Lacunar ischaemic stroke (N = 36)**	**Non-lacunar ischaemic stroke (N = 73)**
CT or MR imaging	101 (93)	35 (97)	66 (90)
CT imaging	70 (64)	22 (61)	48 (66)
Median days to CT imaging* (IQR)	2 (1-4)	4 (1-5)	1 (0-4)
MR imaging	59 (54)	23 (64)	36 (50)
Median days to MR imaging* (IQR)	20 (9-32)	18 (5-31)	21 (1-33)
CT and MR imaging	28 (26)	10 (28)	18 (25)

* Time from onset of symptoms to imaging. CT = computed tomography; MR = magnetic resonance; IQR = interquartile range

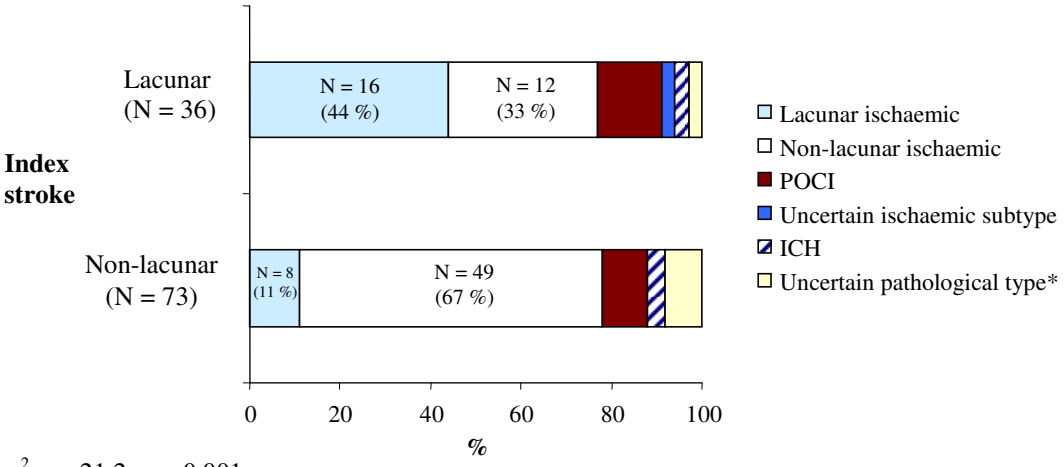
Table 8.5 Brain imaging characteristics of all patients with recurrent ischaemic stroke

Recurrent stroke subtype	Brain imaging performed			Visible relevant infarct on CT and / or MR imaging (%)
	CT (%)	MR (%)	CT and MR (%)	
LACI (n = 24)	11 (46)	17 (71)	4 (17)	16 (67)
TACI (n = 14)	14 (100)	2 (14)	2 (14)	14 (100)
PACI (n = 47)	33 (70)	31 (66)	17 (36)	36 (77)
POCI (n = 12)	9 (75)	8 (67)	5 (42)	9 (75)
All (n = 97)	67 (69)	58 (60)	29 (30)	75 (77)

CT = computed tomography; MR = magnetic resonance; LACI = lacunar infarction; TACI = total anterior circulation infarction; PACI = partial anterior circulation infarction; POCI = posterior circulation infarction

Overall, the distributions of recurrent subtypes following lacunar versus non-lacunar ischaemic stroke subtypes were significantly different (χ^2 test: p = 0.001; Figure 8.9).

Figure 8.9 Recurrent stroke subtype patterns, according to type of baseline ischaemic stroke



χ^2_{5df} = 21.2; p = 0.001

POCI = posterior circulation ischaemic stroke; ICH = intracerebral haemorrhage

The risk of a lacunar recurrence was six times greater following a lacunar than a non-lacunar ischaemic stroke at baseline (OR 6.50, 95% CI 2.43 to 17.52). This association attenuated only slightly and remained statistically significant after adjusting for age, sex and whether patients were on antiplatelet or anticoagulant

therapy at the time of their recurrent stroke (OR 5.39, 95% CI 1.79 to 16.2). The risk of a non-lacunar recurrence was reduced by more than 70% among patients with lacunar compared with non-lacunar stroke at baseline (OR 0.24, 95% CI 0.10 to 0.57), with little change after adjusting for age, sex, and antiplatelet and anticoagulant therapy at stroke onset (adjusted OR 0.27, 95% CI 0.11 to 0.67). When I repeated these analyses in a sensitivity analysis including only those patients who had a recurrent stroke after the acute period (> 30 days post-stroke), I found very similar results to those in the primary analysis, with the risk of a lacunar recurrence about 5 times greater following a lacunar compared with a non-lacunar ischaemic stroke at baseline (adjusted OR 4.97, 95% CI 1.51 to 16.4), and a lower risk of a non-lacunar recurrence following lacunar as compared with non-lacunar ischaemic stroke (adjusted OR 0.36, 95% CI 0.14 to 0.96).

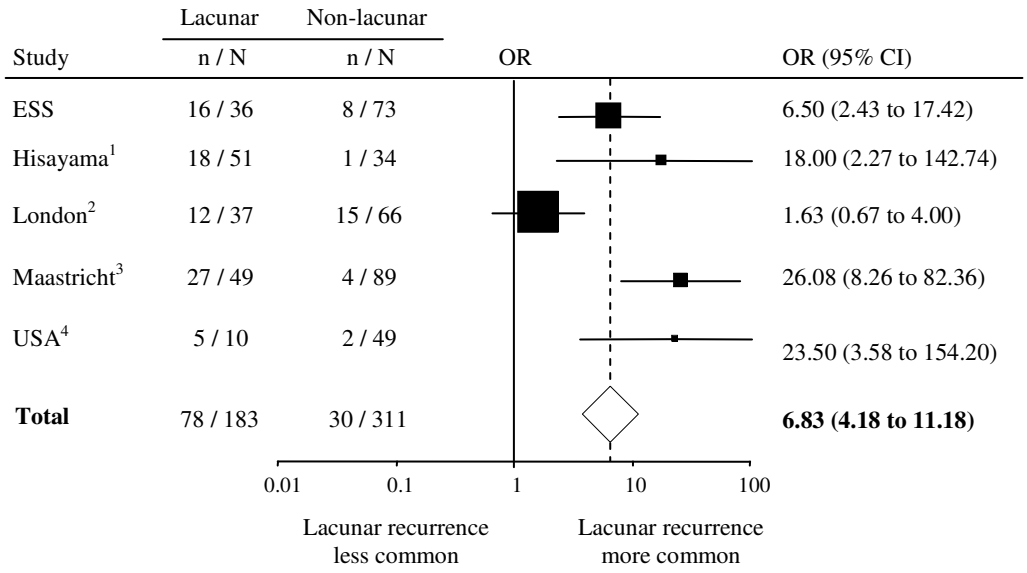
8.4.7 Meta-analysis of recurrent stroke subtype patterns

In my previous systematic review and meta-analysis of outcome studies, I identified four studies that reported on patterns of recurrent stroke subtypes following lacunar and non-lacunar ischaemic stroke (De Jong *et al*. 2004; Hata *et al*. 2005; Hillen *et al*. 2003; Nadeau *et al*. 1993). After combining data from these studies with unadjusted data from the Edinburgh Stroke Study, I found a six-fold increase in the odds of a lacunar recurrence following a lacunar compared with a non-lacunar ischaemic stroke at baseline (OR 6.83, 95% CI 4.18 to 11.18; Figure 8.10). There was however substantial heterogeneity between studies (I^2 = 77%) which could largely be explained by the results of one study in which the proportion of recurrences that were lacunar following non-lacunar ischaemic stroke at baseline was much higher (23%) than in the other three studies (3% to 4%) and in the ESS (11%) (Hillen *et al*. 2003).

Similarly, the odds of a non-lacunar recurrence among patients with a lacunar versus non-lacunar stroke at baseline was significantly lower (OR 0.21, 95% CI 0.14 to 0.32; Figure 8.10), with substantial heterogeneity again explained by the results of one study (Hillen *et al*. 2003). One notable difference between this study and the others is the definition of recurrent stroke used. In the former, recurrences that occurred within 21 days of the index stroke and in the same part of the brain as the first stroke were excluded. This may have biased the results, leading to an underestimation in this study of the extent to which recurrent stroke subtypes may breed true. Brain imaging rates among index and recurrent strokes were similar to those in the other included studies (but lower than in the ESS), but there may be other unidentified methodological differences in this study which may explain this different recurrent stroke subtype pattern, such as quality of clinical assessment; time from stroke onset to assessment; time from stroke onset to brain imaging and type of brain scan. A combination of these may have led to greater misclassification of ischaemic stroke subtypes.

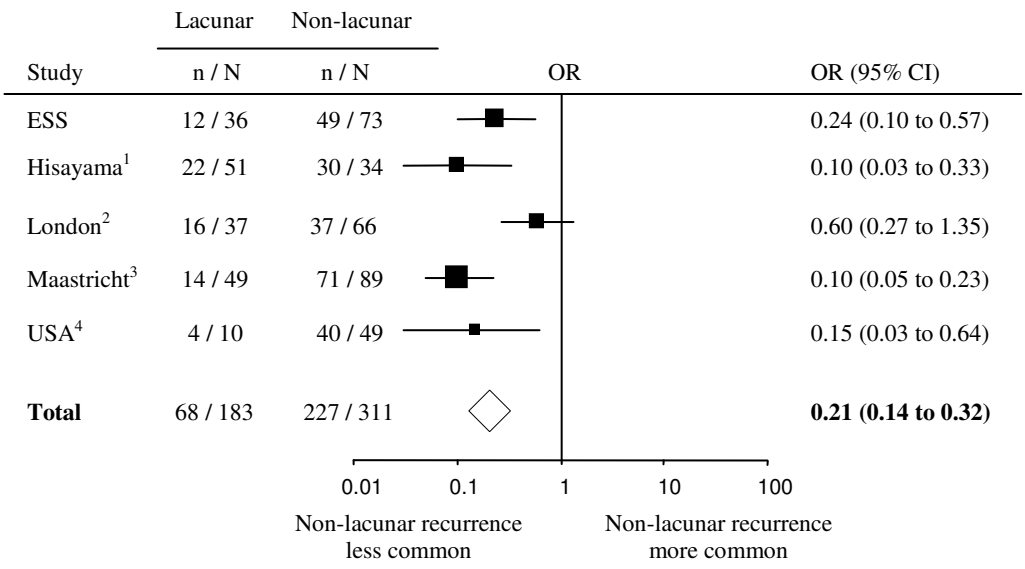
Figure 8.10 Meta-analysis of (a) risk of lacunar recurrence and (b) risk of non-lacunar recurrence, following lacunar versus non-lacunar ischaemic stroke at baseline

(a)



Heterogeneity between studies: $I^2 = 77\%$

(b)



Heterogeneity between studies: $I^2 = 65\%$

In (a), n = number of patients with a lacunar recurrence and N = total number of either lacunar or non-lacunar patients who had a recurrence.
In (b), n = number of patients with a non-lacunar recurrence and N = total number of either lacunar or non-lacunar patients who had a recurrence.
Open diamond represents the pooled summary estimate. OR = odds ratio; CI = confidence interval; ESS = Edinburgh Stroke Study.
[1]Hata *et al*. 2005; [2]Hillen *at al*. 2003; [3]de Jong *et al*. 2004; [4]Nadeau *et al*. 1993

8.4.8 Misclassification of baseline and ischaemic stroke subtypes

In my primary analysis 509 / 809 patients had a visible relevant infarct on their scan, 64 of whom were allocated to a different comparison group than would have been the case based on their clinical syndrome alone. Applying the proportion misclassified (64 / 509) to the 300 patients with no visible relevant infarct on their brain scan gave an estimated 42 / 809 (5%) patients residually misclassified at baseline. Slightly fewer – 4 / 97 (4%) – recurrent strokes were potentially misclassified. Among baseline and recurrent strokes, the degree of misclassification was similar in the lacunar and non-lacunar comparison groups.

8.5 Discussion

My analyses of data from the Edinburgh Stroke Study revealed no difference in the long-term risk of recurrent stroke between patients with lacunar compared with non-lacunar ischaemic stroke. However, the very early risk of recurrence was almost certainly lower in patients with lacunar stroke, confirming results of previous studies (Lovett *et al*. 2004) and probably reflecting a lower prevalence of active thromboemboli early after lacunar compared with non-lacunar ischaemic stroke. I also confirmed that recurrent stroke subtypes do tend to breed true, even after adjusting for potentially confounding effects of age, gender and secondary stroke prevention treatment at onset of recurrent stroke, which had not been accounted for in my systematic review and meta-analysis, or in previous individual studies. And when I examined recurrent stroke subtype patterns after having excluded any recurrences that occurred in the first month, I found very similar results to those in my primary analysis, which indicates that in the long term, after presumed healing of any unstable atherosclerotic plaques, recurrent stroke subtypes still appear to breed

true. The similarity between adjusted and unadjusted results provides methodological justification for my meta-analysis of unadjusted data from published studies, the results of which confirm and strengthen the findings from the Edinburgh Stroke Study. Finally, I observed a lower MI risk following lacunar versus non-lacunar ischaemic stroke, in keeping with my previous findings of a lower prevalence of IHD among patients with lacunar as compared with non-lacunar ischaemic stroke.

8.5.1 Study strengths

The Edinburgh Stroke Study and my analysis of outcome events benefit from a number of methodological strengths. First we recruited a large study population at baseline, allowing us to collect a relatively large number of outcome events. In particular, we identified over five times as many MI events as reported in the only previous published study of MI risk among both lacunar and non-lacunar ischaemic stroke subtypes (Landi *et al*. 1992).

Second, an important feature of our study is the high proportion of patients who had brain imaging following baseline and recurrent strokes (100% and 93% respectively). Where reported in previous studies, the proportion of patients with recurrent stroke in whom brain imaging was performed was much lower (40-65%), with no study reporting the use of DW MR imaging. The extensive use of brain imaging (particularly DW MRI) in our study allowed us to classify recurrent stroke subtypes with a higher degree of accuracy than in previous similar studies, thereby reducing misclassification of ischaemic stroke subtypes. However, some misclassification of stroke subtypes is inevitable, since not all lesions are visible on brain imaging. I estimated the extent of misclassification to be low in patients included in my primary analyses, and given that the proportion of misclassified patients in both comparison

groups was similar, I am unlikely to have overestimated - but may have underestimated – any true differences in outcome.

Third, we used an unbiased definition of recurrent stroke since we did not automatically exclude those patients with an early recurrence in the same territory of the brain as the index events, as many previous studies have done. We therefore limited underestimation of the early risk of recurrence (Coull & Rothwell 2004) and potential bias in determining recurrent stroke subtype patterns. Clinicians were not specifically blinded to the subtype of the index stroke when classifying the subtype of the recurrent stroke, to allow them to distinguish between residual neurological signs due to the index stroke and new neurological signs due to the recurrent stroke. Knowledge of the nature of the index event may influence assignment of the recurrent subtype, particularly when there is uncertainty as to the subtype of recurrence, but we were able to minimise this potential bias in our study through our extensive use of brain imaging.

Finally, we used multiple overlapping follow-up methods to maximise ascertainment of outcome events. My analysis of the completeness of follow-up was, however, complicated by this use of multiple overlapping methods. Ideally, I would have analysed success of follow-up using a capture-recapture analysis approach, but I was unable to do this because we did not routinely record the route(s) by which we identified a recurrent event. Although we had not routinely recorded the last date of contact with each patient, I was able to modify the approach by Clark *et al*. to estimate the minimum completeness of follow-up by determining the completeness of follow-up by postal questionnaire. It is important to note that the calculated completeness is a minimum estimate of follow-up completeness, because it does not

account for all methods of follow-up used. However, the advantage of this analysis is that I was able to investigate whether follow-up completeness differed between patients with lacunar and non-lacunar ischaemic stroke, and hence address whether any difference in outcome between these groups was biased by incomplete follow-up contact. It is reassuring that completeness of follow-up was high, and was similar in the comparison groups included in my primary analysis. However, this analysis does not of course reveal to what extent events may have been missed due to lack of reporting of events by patients, their GPs and others.

8.5.2 Study limitations

The Edinburgh Stroke Study and my analyses of outcome do have a few limitations. Although we used multiple overlapping methods of follow-up, we may have under-ascertained vascular events. Despite our definition of recurrent stroke, the early recurrence rates were quite low in comparison to those of similar previous studies, suggesting that we may have under-ascertained recurrences, particularly during the early period (Lovett *et al*. 2004). This may partly reflect our recruitment of patients several days (median 9) after stroke onset, effectively excluding from our first-ever stroke cohort some patients who had already had a very early recurrence. Although time to recruitment of patients with lacunar stroke was somewhat longer (median 12 days) than for those with non-lacunar stroke (median 7 days), the delay to recruitment would have caused in particular an underestimate of the very high recurrence rate in the first few days after non-lacunar (mainly large artery) ischaemic stroke, so diminishing the early excess of recurrences detected by our study among those with non-lacunar versus lacunar strokes. In addition, we may have been more likely to have missed some recurrent stroke or MI events occurring among patients

with a severe stroke at baseline, where ascertainment of further events may have been complicated by patients' co-morbidities, or where patients or doctors may have been less likely to report possible further events to our stroke study team. However, the results of my primary analysis were unchanged in a sensitivity analysis comparing lacunar patients with mild cortical (PACI) patients for risks of recurrence and MI. We are far less likely to have incorrectly included false positive outcome events, since for all outcomes we either assessed patients face-to-face or thoroughly reviewed their medical notes. Furthermore, it is also reassuring that the incidence of MI in our study is comparable to the incidence of MI in ischaemic stroke patients in previous published studies (Touze *et al*. 2005).

Second, although this is the largest study of the risk of MI among different ischaemic stroke subtypes to date, the relatively low incidence of MI still limited the reliability and precision of comparisons between lacunar and non-lacunar patients, and prevented full adjustment for potential confounders.

Third, in my primary analyses I may have included a small number of patients in the lacunar group whose stroke may have been caused by thromboemboli rather than small vessel disease (since more than one potential aetiology is present in some patients). However the results of my primary analyses remained unchanged in a sensitivity analysis where I compared stroke subtypes according to their presumed aetiological cause.

Finally, there was substantial heterogeneity between studies in my meta-analysis of recurrent stroke subtypes, but this could be explained by the results of one study (Hillen *et al*. 2003) in which the definition of recurrent stroke may have biased the

results and led to underestimation of the degree to which recurrent stroke subtypes breed true

8.5.3 Conclusion

In conclusion, my findings considerably strengthen the existing evidence for a lower risk of stroke recurrence early after lacunar ischaemic stroke, reflecting the lower prevalence of active thromboemboli early after lacunar versus non-lacunar stroke. My novel finding of a lower risk of MI following lacunar as compared with non-lacunar ischaemic stroke provides further epidemiological evidence to suggest that many lacunar ischaemic strokes may be caused by a distinct, non-atherothrombotic arteriopathy. Because this last finding was based on relatively small numbers of MI events (albeit a much larger number than previously published), it would be very helpful to confirm these results with a pooled analysis of data from stroke cohorts similar to the Edinburgh Stroke Study, with well characterised baseline ischaemic stroke subtypes and follow-up for MI.

Finally, data on recurrent stroke subtype patterns in the Edinburgh Stroke Study suggest that recurrent stroke subtypes tend to breed true to type, adding further support to the notion of a distinct lacunar arteriopathy.

D. Summary and Conclusions

Chapter 9. Conclusions and implications for further research

9.1 Summary of the epidemiological evidence for a distinct lacunar arteriopathy

My comparisons of the epidemiology of ischaemic stroke subtypes revealed differences in the risk factor profiles and risks of recurrent vascular events between patients with lacunar as compared with non-lacunar ischaemic stroke which suggest that many (and perhaps most) lacunar ischaemic strokes are caused by a distinct, non-atherothrombotic small vessel disease.

9.1.1 Risk factor profiles

In my systematic literature review of studies of the risk factor profiles of ischaemic stroke subtypes, I found evidence of classification bias in many studies, where systematic error was introduced through the use of ischaemic stroke subtype classification methods in which risk factors are included in the definitions of stroke subtypes. For some risk factors this led to overestimation of the assciation with ischaemic stroke subtype, and for others it resulted in an apparently stronger association with lacunar compared with non-lacunar ischaemic stroke which was not apparent in studies that used risk factor-independent classification methods.

In my analyses of individual patient data pooled from the Edinburgh Stroke Study and from other similar stroke registers, I was able to overcome both the methodological shortcomings of most previous studies of risk factor-stroke subtype associations and the limitations of my meta-analyses of these existing published

studies. In this large pooled data project I confirmed that atrial fibrillation (AF) and severe carotid stenosis are found relatively infrequently in patients with lacunar ischaemic stroke, and are much less prevalent than in patients with non-lacunar ischaemic stroke. This strongly suggests that emboli from the heart or proximal arteries are likely to be the cause of only a minority of lacunar strokes, especially given the fact that where sources of emboli such as AF are present, they may be incidental (i.e. not causal) in some patients. The probable non-causal role of carotid artery stenosis has been demonstrated in studies comparing the severity of internal carotid artery stenosis on the symptomatic (ipsilateral) side versus the asymptomatic (contralateral) side within the same patient. Most studies found no difference in severity of carotid stenosis in the symptomatic versus non-symptomatic side in patients with lacunar ischaemic stroke, indicating that carotid stenosis may be coincidental (Mead *et al*. 2002).

Interestingly, the likelihood of emboli reaching the small peforating arteries supplying the deep parts of the brain has been investigated in an experimental study, in which the authors injected varying sizes of agarose emboli into the internal carotid arteries of nine monkeys. They found that although very small embolic particles could enter deep penetrating arteries in the brain, they did so infrequently, with up to just 6% of embolic particles entering the lenticulostriate arteries and the remainder entering cortical arteries (Macdonald *et al*. 1995).

My findings also suggest that prior ischaemic heart disease (IHD), for which the relationship with ischaemic stroke subtype was far less clear in previous published studies, is also less common among patients with lacunar than non-lacunar ischaemic stroke. If we consider IHD, and indeed carotid artery stenosis, to be markers of

systemic atherosclerosis, these results further suggest that a non-atherosclerotic arteriopathy may underlie many lacunar strokes. Further evidence supporting this concept comes from studies of intracranial artery blood flow velocity, blood flow reversal and vessel stenosis or occlusion. One study reported a lower frequency of some or all of these abnormalities (as determined by transcranial doppler investigation) in the middle and anterior cerebral arteries of patients with lacunar ischaemic stroke compared with patients with total or partial anterior circulation infarction (Mead *et al*. 2000). Although some of these abnormalities may be due to downstream effects of internal carotid artery stenosis (which, as I reported in this thesis, is more common in patients with non-lacunar than lacunar ischaemic stroke) rather than intracranial large artery stenosis, these findings do suggest that intracranial large artery atherosclerosis seems to be less common among patients with lacunar ischaemic stroke. Given the lower frequency of carotid, cardiac and intracranial large artery stenosis among lacunar compared with non-lacunar patients, it seems unlikely that lacunar ischaemic stroke is largely caused by atherosclerosis in the small penetrating arteries.

In contrast to widespread belief, I found that diabetes does not appear to be more important in the aetiology of lacunar ischemic stroke than in other types of ischaemic stroke. In my combined individual patient data analysis I also found no differences in the prevalence of prior hypertension between patients with lacunar versus non-lacunar stroke, although, when I combined these data with those from similar published studies, prior hypertension was marginally more common in patients with lacunar stroke. Thus the epidemiological evidence does not support the view that

hypertension is substantially more important in the aetiology of lacunar relative to non-lacunar ischaemic stroke

9.1.2 Risks and patterns of vascular outcomes

In my systematic review of studies reporting on risks of death and recurrent vascular events among patients with different ischaemic stroke subtypes I found that risk of death was higher among patients with lacunar compared with non-lacunar ischaemic stroke in the short term, with the difference attenuating, but persisting, in the long term. On further investigation of this using data from the ESS, I found that this difference in risk of death is far greater at one month post-stroke than at later time periods, and, at all time periods, is at least partly explained by stroke severity. Thus, differences in risk of death between stroke subtypes do not greatly inform on differences in underlying arterial pathologies.

In my systematic review and meta-analyses, recurrent stroke risk appeared to be lower among patients with lacunar stroke in the first month post-stroke, with no difference in risk thereafter. Similarly, in the ESS there was a trend towards a lower recurrence risk following lacunar compared with non-lacunar stroke in the first month, with no apparent difference thereafter. Given the lower prevalence of embolic sources in lacunar patients, this probably reflects the lower prevalence of active thromboemboli early after lacunar compared with non-lacunar ischaemic stroke.

When reviewing the published literature, I found few studies presenting data on recurrent stroke subtype patterns, and sparse data on risk of myocardial infarction (MI) following different ischaemic stroke subtypes. Our data on recurrent stroke subtype patterns and MI risk in the Edinburgh Stroke Study therefore make a

significant additional contribution to existing published data. My results suggested a trend towards a reduced rate of MI following lacunar compared with non-lacunar ischaemic stroke, which is in keeping with my findings of a lower prevalence of IHD in lacunar patients, and provides further support for a non-atherothrombotic lacunar arteriopathy underlying many lacunar strokes.

Recurrent stroke subtype patterns have only been reported in a handful of published studies and have had some important limitations. In the ESS our careful characterisation of both baseline and recurrent stroke subtypes and rigorous follow-up of patients means that our study is the most methodologically robust study in which recurrent stroke subtype patterns have been analysed to date. We observed that recurrent ischaemic strokes were more likely to be of the same subtype (lacunar or non-lacunar) as the index event, a finding which was largely in agreement with results of existing studies, adding substantial support to the notion that recurrent stroke subtypes breed true to type and providing additional epidemiological evidence for a distinct lacunar arteriopathy.

9.2 Implications for, and direction of, future research

9.2.1 The need for accurate classification of ischaemic stroke subtypes

The results of my comparisons of the risk factor profiles of lacunar versus non-lacunar ischaemic stroke have implications for the way in which patients with lacunar ischaemic stroke in particular are classified. First, the epidemiological evidence indicates that clinicians should not be guided by the presence or absence of hypertension and diabetes when classifying ischaemic stroke subtypes.

Second, my investigation of the effect of stroke subtype classification method on comparisons of risk factor profiles of different ischaemic stroke subtypes reveals the

impact that the classification system can have on the results of research studies. The resulting bias which I demonstrated in my meta-analyses in chapter three highlight the important point that in research studies, the classification method used should be appropriate to the research question being addressed. The issue of how best to classify ischaemic stroke subtypes is therefore clearly an important one, particularly in clinical research, and should be given careful consideration.

Accurate and unbiased classification of ischaemic stroke subtypes is not only relevant to observational studies such as those analysed and discussed in this thesis. There is an increasing interest at present in the role of genetic factors in the pathogenesis of ischaemic stroke and its subtypes. The most efficient and frequently used approach to study this is the genetic association study, where the frequencies of DNA sequence variants (allelic polymorphisms or the different genotypes they give rise to) are compared between cases and controls. Although there is a rapidly growing interest in the field of stroke genetics, the findings to date have been disappointing with few replicable and robust associations identified. This may be partly explained by poor study methodology. For example, existing studies may have been too small, leading to false-positive or false-negative results (Dichgans & Markus, 2005). Furthermore, and most pertinent to this discussion, patients need to be well characterised or "phenotyped" in terms of the ischaemic stroke subtype. Poorly characterised ischaemic stroke subtypes may contribute to the failure to identify and reproduce true genetic associations (Dichgans & Markus, 2005).

Another research area to which the classification of ischaemic stroke subtypes is particularly relevant is that of randomised controlled clinical trials. With the growing understanding of the complexity of the causes of ischaemic stroke and the

recognition that ischaemic stroke subtypes are likely to differ in their underlying arterial pathologies, there is a need to determine the effectiveness of current thrombolytic and anti-thrombotic therapies in patients with lacunar ischaemic stroke, and to tailor treatment regimes to optimise their effect in patients with lacunar ischaemic stroke (Benavente & Hart 2004) . The use of these treatments is currently based on clinical trials that either failed to distinguish between ischaemic stroke subtypes, or were statistically under-powered to detect differences in treatment effect between stroke subtypes. There is also a growing interest in the development of therapies that are more targeted to treating and/or preventing specific stroke subtypes (Aslanyan *et al*. 2007). Future clinical trials need to be as well powered as possible to detect differences in treatment effect between these subtypes. Just as importantly, they should also be designed to distinguish accurately between ischaemic stroke subtypes, thereby reducing ischaemic stroke subtype misclassification which may otherwise contribute to the failure to detect important differences in treatment effect between groups of patients.

9.2.2 Improving on existing ischaemic stroke subtype classification methods

There is a need to improve upon the accuracy of the classification of ischaemic stroke subtypes. While the nature of stroke makes it impossible to accurately diagnose and categorise every patient with this disorder, there may be ways of further developing existing classification methods, to minimise this misclassification. Some researchers favour the use of an aetiological classification, which they consider to be more informative and more accurate than the OCSP classification (Dichgans & Markus, 2005). However, it must be recognised that the most frequently used aetiological classification – the TOAST classification – does have some major

limitations, including the need for extensive investigations (which may limit its use in particular centres where certain clinical investigations are not available or routinely used); variation in the interpretation and application of the classification; and the large proportion of patients who are placed in the "undetermined cause" category (even with complete investigation). The latter limitation is currently being addressed by one group who, through a modified, extended version of the original TOAST classification, are attempting to reduce the proportion of patients who are labelled as having an undetermined cause (Ay H *et al*. 2005; Ay H *et al*. 2007). The performance of this classification, particularly within different clinical settings, remains to be established.

An alternative classification approach worthy of further development and assessment is one which combines the clinical and imaging-based classification system with an aetiological component, such as the algorithm described in chapter 7, which I devised for the purpose of retrospectively assigning an aetiological classification to patients in the ESS. In such an approach, the clinical and imaging-based classification would form the basic classification level, after which the classification becomes more aetiologically refined, with the incorporation of findings from additional investigations. Such a multilevel approach would allow most stroke patients to be classified as accurately as possible in the majority of clinical settings, but would incorporate an option for increasing the degree of refinement where suitable investigations are available and performed, perhaps for the purposes of specific research studies.

9.2.3 Minimising ischaemic stroke subtype misclassification

In all classification methods there will inevitably be some degree of misclassification. The OCSP classification is easily and quickly applied in all clinical settings, predicts death, disability and recurrent stroke, and, as demonstrated in this thesis, does relate to a large extent to the underlying aetiology. It therefore remains a very useful method of classifying ischaemic stroke subtypes, and is especially useful in settings where clinical investigations such as brain imaging or echocardiography, or even more advanced investigations such as DW MR brain imaging, are less readily available. However, there is a need to minimise misclassification between ischaemic stroke subtypes and particularly between lacunar and small cortical ischaemic stroke. One method of reducing this misclassification is to perform advanced DW MR imaging rather than CT brain imaging in patients with lacunar or mild cortical ischaemic stroke or when patients present late. In the acute period, CT imaging is known to be less sensitive than diffusion weighted (DW) MR imaging for small acute infarcts (Lansberg *et al*. 2000), and conventional MR imaging has been shown to be less sensitive than conventional MR imaging with DW sequences when applied several weeks after the stroke event (Kier *et al*. 2004). The use of MR imaging with DW sequences is therefore likely to reduce misclassification between stroke subtypes. However, the extent to which CT brain imaging (which is far less expensive and more accessible than MR imaging) underestimates the degree of misclassification between lacunar and mild cortical ischaemic stroke relative to DW MR imaging needs to be investigated. No study has yet compared CT brain imaging with DW MR imaging performed at the same time (as near as possible) to assess ischaemic stroke subtype

misclassification. Such a study would be helpful in determining how far misclassification of ischaemic stroke subtypes can be reduced through the use of advanced DW MR imaging.

9.2.4 Effects of ischaemic stroke subtype misclassification

In my analyses of individual patient data, the degree of misclassification of ischaemic stroke subtypes was similar among patients with lacunar and non-lacunar ischaemic stroke, and, assuming that this misclassification is independent of risk factor status (which seems likely),will have probably led to an underestimation of risk factor-stroke subtype associations, moving the odds ratio estimates closer to the null (Copeland *et al*. 1977). It is therefore possible that we may have slightly underestimated the true odds ratios for some risk factor-stroke subtype associations. It may be possible to adjust effect estimates for this misclassification of covariates (Thomas *et al*. 1993) but unfortunately the investigation and applicability of such methods to my risk factor-ischaemic stroke subtype associations was beyond the scope of my thesis. However, it would be interesting to investigate such statistical approaches in future analyses of these data.

9.2.5 Classification of risk factors

One of the limitations of the collaborative individual data project where I compared the risk factor profiles of patients with lacunar versus non-lacunar ischaemic stroke is the way in which some risk factors were defined. There will certainly have been some misclassification of prior hypertension and diabetes mellitus in particular, partly because they were ascertained retrospectively (after the stroke event occurred). We may have misclassified patients who actually had undiagnosed hypertension and diabetes as not having these risk factors. Also, given that hypertension and diabetes

mellitus can both be subcategorised further, our definitions may have been too broad, thereby obscuring any associations between subgroups of these exposures and ischaemic stroke subtypes. For example, the severity and duration of exposure to raised blood pressure, extreme fluctuations in blood pressure, and whether a patient has Type I or Type II diabetes mellitus and their duration of exposure to diabetes may each be important.

Presence of undiagnosed hypertension may be detected by measuring post-stroke blood pressure, but the reliability of these measurements as indicators of pre-stroke hypertension is questionable given that the stroke itself often affects blood pressure. Duration of exposure to hypertension is much harder to determine without having obtained repeat blood pressure measurements in healthy subjects followed prospectively for the occurrence of stroke. Severity and/or duration of hypertension may be reflected in the presence or absence of left ventricular hypertrophy - detectable by electrocardiogram or echocardiogram, with differing degrees of sensitivity - although it should be remembered that factors other than raised blood pressure can cause left ventricular hypertrophy (Dunn & Pfeffer 1999). These data are available in some of the patients in the Edinburgh Stroke Study and could be included in further sensitivity analyses of the effect of differing definitions of hypertension on associations between risk factors and ischaemic stroke subtypes. Given the continuous log linear relationship between increasing blood pressure and stroke (Prospective Studies Collaboration 2002), we will also have lost information by dichotomising patients as being hypertensive or not (Altman & Royston, 2006), and it would almost certainly be more informative to analyse blood pressure as a continuous variable. However, this can only be done reliably in prospective studies

of healthy subjects where blood pressure has been measured at baseline (with repeat measurements in a subset of subjects to allow adjustment for regression dilution bias) prior to the occurrence of stroke outcomes. The relationship between subgroups of diabetes and specific ischaemic stroke subtypes might be investigated in more depth in future projects which take advantage of the existence of the Scotland-wide clinical stroke audit (in which details of stroke events are collected) and diabetes registers. In the longer term, useful data on the relationship between blood pressure, other risk factors and different ischaemic stroke subtypes may be obtained from new, large prospective studies such as the UK BioBank project. In the latter study, extensive baseline data and blood samples on 500,000 middle-aged people are being collected with plans to follow up for outcome events for most common disease including stroke over the next few decades (Elliott *et al*. 2008). Such studies will be very informative about risk factor-ischaemic stroke subtype relationships, provided that sufficient details of the subtype of ischaemic strokes that occur are collected.

9.2.6 Myocardial infarction following lacunar ischaemic stroke

Despite making a substantial contribution to the existing published data on MI risk across different ischaemic stroke subtypes, the number of MI events in our study was still too low to allow appropriate adjustment for potential confounding factors and to draw definite conclusions about the relationship between risk of MI and lacunar compared with non-lacunar ischaemic stroke. My results need to be confirmed in a meta-analysis of individual patient data from the Edinburgh Stroke Study and other studies that have similarly collected data on well characterised ischaemic stroke subtypes and MI during follow-up.

9.2.7 Two subtypes of small vessel disease?

An interesting hypothesis has been presented which proposes that patients who present with a lacunar ischaemic stroke and who have a single lacunar infarct on brain imaging represent a discrete clinical subgroup from those patients who present with a lacunar ischaemic stroke but have multiple, usually asymptomatic, lacunar infarcts on brain imaging, the view being that these two groups of patients reflect two distinct arterial pathologies (Boiten *et al*. 1993). There is some epidemiological evidence to support this theory. Hypertension and diabetes have been reported in a few studies as being more common in lacunar ischaemic stroke patients who have multiple, usually asymptomatic, lacunar infarcts on brain imaging than lacunar ischaemic strokes patients with a single lacunar infarct on brain imaging (Boiten *et al*. 1993; Mast *et al*. 1995; Machizuki *et al*. 1997). And there is evidence of differences in outcome in terms of death, recurrent stroke and disability between these two groups of patients (De Jong *et al*. 2002). However, these findings are based on results from just a few small studies which largely used CT brain imaging to identify lacunar infarcts, and did not include a control group of non-lacunar stroke patients.

One study also reported that leukoaraiosis is statistically significantly more common among patients with multiple asymptomatic lacunar infarcts than in patients without asymptomatic lacunar infarcts (Boiten *et al*. 1993). A related finding is that hypertension may be more common in patients with lacunar ischaemic stroke and white matter hyperintensities (leukoaraiosis) on brain imaging, than in patients with lacunar ischaemic stroke without leukoaraiosis (Khan *et al*. 2007). The relationship between the underlying arteriopathy of lacunar ischaemic stroke and leukoaraiosis

remains unclear. It has been proposed that a cerebral small vessel endothelial dysfunction may contribute to the development of both these conditions (Wardlaw *et al*. 2003). Alternatively, it has been proposed that isolated lacunar infarction in patients without leukoaraiosis may result from atheroma in the small perforating arteries, whilst small vessel endothelial dysfunction might be responsible for multiple small lacunar infarcts and leukoaraiosis (Markus, 2008).

The identification of and discrimination between subgroups of ischaemic stroke subtypes may be especially useful in the refinement of ischaemic stroke phenotypes for the purposes of maximising insight into the underlying arterial pathologies at the molecular and genetic level, and is certainly worthy of further investigation. The existing epidemiological evidence supporting the notion of two small vessel disease subtypes stems largely from a small number of observational studies comparing the clinical features and risk factors of patients with lacunar ischaemic stroke with and without asymptomatic lacunar infarcts. Many of these studies have relied on CT brain imaging in the identification of lacunar infarcts (and white matter hyperintensities), included small numbers of patients, and did not always include a cortical stroke control group. This area could be explored further using baseline and follow-up data from patients who had DW MRI in the Edinburgh Stroke Study, to determine whether different types of lacunar ischaemic stroke can be distinguished. Detailed imaging data (such as presence of asymptomatic lacunar infarcts) was not recorded at the time of data collection for the Edinburgh Stroke Study, but has since been collected retrospectively for patients who underwent MRI. It might also be appropriate to combine our data from other studies of stroke patients that have

similarly used MRI, to increase numbers of patients and power to detect moderate differences in risk factor prevalence and outcome.

9.3 A multi-disciplinary approach to the study of lacunar ischaemic stroke

The difficulties inherent in studying the aetiology of lacunar ischaemic stroke makes identification of the nature of the underlying small vessel arteriopathy very challenging. My investigation of the epidemiological differences of ischaemic stroke subtypes has been highly informative and makes an important contribution to our understanding of lacunar stroke pathology. It complements other approaches to studying the arteriopathy of lacunar stroke and highlights ways to improve the methodology of future research. That research should continue to be multi-disciplinary if we are to make further progress in understanding the arteriopathy of lacunar stroke. Interesting findings are currently being generated through advanced brain imaging research, with the early results proving very promising. This research uses cutting-edge brain imaging techniques to investigate the permeability of arteries in the brain, and recent results do indicate a possible role of increased blood-brain-barrier "leakiness" (perhaps as a result of endothelial dysfunction) in patients with lacunar compared with non-lacunar ischaemic stroke (Wardlaw *et al*., 2009). Although genetic studies have identified associations between factors connected with endothelial function and lacunar ischaemic stroke, few of these have been robust, replicable assocations (Markus, 2008). Furthermore the complex interaction between environmental and genetic factors adds to the difficulty of identifying genetic factors important to the aetiology of lacunar stroke. It remains to be seen whether large multicentre collaborative efforts, with improved methodology, will prove to be more successful.

Finally, although autopsy studies of lacunar stroke are fraught with a number of drawbacks, there is perhaps a need for modern day pathological autopsy studies which, in combination with the improved collection of clinical data and advanced brain imaging now available, may prove more fruitful than the pathological studies from 40-50 years ago. This would, however, require a renewed enthusiasm for the value of such studies, and a reversal of the current decline in autopsy rates.

9.4 Conclusion

My comparisons of the epidemiology of different ischaemic stroke subtypes suggest that a distinct, non-atherothrombotic arteriopathy may underlie many lacunar ischaemic strokes. These findings support other lines of evidence for a distinct lacunar arteriopathy, and highlight the need for further research into lacunar ischaemic stroke to identify the main pathological abnormality and its molecular mechanism. Lacunar ischaemic stroke is a particularly complex condition to study, not least because it can be caused by multiple pathologies which are not necessarily mutually exclusive within a single patient, and which share common multifactorial determinants. This complexity means that a multi-disciplinary approach, including epidemiological, pathological, molecular, genetic and brain imaging studies, is needed to identify the precise nature of the vascular pathology underlying most lacunar ischaemic strokes.

Appendices

Appendix 1 Oxfordshire Community Stroke Project clinical syndromes

Clinical syndrome	Details	Presumed principal pathology (in ischaemic stroke)
Lacunar	Any of: Pure motor stroke Pure sensory stroke Sensorimotor stroke } The relevant deficit should involve at least two contiguous areas out of three of the whole of the face, arm and leg* Ataxic hemiparesis There should be no: visual field deficit new disturbances of higher cerebral function signs of brainstem disturbance†	Small vessel disease
Partial anterior circulation syndromes	Any of: Motor / sensory deficit plus hemianopia Motor / sensory deficit plus new higher cerebral dysfunction New higher cerebral dysfunction plus hemianopia New higher cerebral dysfunction alone Pure motor / sensory deficit less extensive than for lacunar syndromes (e.g. monoparesis (such as hand weakness))	1. Cardioembolism 2. Atherothrombosis (large vessel disease)
Total anterior circulation syndrome	All of: Hemiplegia or severe hemiparesis Hemianopia New disturbance of higher cerebral function (e.g. dysphasia) + / - sensory deficit	1. Cardioembolism 2. Atherothrombosis (large vessel disease)
Posterior circulation syndrome	Any of: Ipsilateral cranial nerve (III-XII) palsy with contralateral motor and/or sensory deficit Bilateral motor and/or sensory deficit Disorder of conjugate eye movement Cerebellar dysfunction without ipsilateral long tract deficit Isolated hemianopia or cortical blindness (disorders of higher cerebral function may also be present, e.g. aphasia)	1. Cardioembolism 2. Atherothrombosis (large vessel disease) 3. Small vessel disease

*i.e. face and arm, arm and leg or all three

†Some brainstem syndromes may be caused by lacunar infarcts (e.g. in the pons or the cerebellum)

(modified from Warlow et al. 2008)

Appendix 2 Description of TOAST classification

Category	Description
Large artery atherosclerosis	• Clinical findings include cortical, cerebellar, or brain stem dysfunction and on brain imaging cortical, cerebellar, brain stem or subcortical lesions >1.5cm are considered to be of potential large artery atherosclerotic origin. • Diagnosis requires supportive evidence by duplex imaging or arteriography of >50% stenosis of an appropriate intracranial or extracranial artery. • Potential sources of cardiogenic embolism, such as AF should be excluded, and history of TIAs in the same vascular territory supports the clinical diagnosis.
Cardioembolism	• Clinical and brain imaging findings are similar to those described for large artery atherosclerosis. • At least 1 cardiac source of embolism, such as AF, must be identified. Previous TIAs in >1 vascular territory supports the diagnosis. • Potential large artery atherosclerotic sources of thrombosis or embolism should be absent.
Lacunar	• Clinical findings of one of the lacunar syndromes should be present. Brain imaging should be normal or show a relevant brain stem or subcortical hemispheric lesion of diameter <1.5cm. • A history of diabetes mellitus or hypertension supports the diagnosis. • Potential cardiac sources of embolism, such as AF, should be absent, and the large extracranial arteries should not demonstrate >50% stenosis.
Undetermined aetiology	Includes patients with ≥2 potential causes of stroke (eg, AF and >50% stenosis of extracranial arteries), patients with no identifiable cause of stroke following complete or incomplete investigation.
Other determined aetiology:	Includes patients with rare causes of stroke (eg, nonatherosclerotic vasculopathies and haematologic disorders).

AF = atrial fibrillation; TIA = transient ischaemic attack

Appendix 3 MedLine literature search strategy

1. cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp cerebrovascular accident/ or exp dementia, vascular/ or exp hypoxia-ischemia, brain/ or exp intracranial arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or exp vasospasm, intracranial/
2. (Stroke$ or cerebrovasc$ or cerebral vasc$).tw.
3. 1 or 2
4. lacun$.tw.
5. ((lacunar or small or subcortical or silent) adj5 (infarct$ or stroke)).tw.
6. (small vessel adj5 (stroke$ or occlusion or disease)).tw.
7. 4 or 5 or 6
8. 3 and 7
9. 9 limit 8 to human

Appendix 4 Embase literature search strategy

1. cerebrovascular disease/ or cerebral artery disease/ or cerebrovascular accident/ or stroke/ or exp carotid artery disease/ or exp brain infarction/ or exp brain ischemia/ or exp occlusive cerebrovascular disease
2. (Stroke$ or cerebrovasc$ or cerebral vasc$).tw.
3. 1 or 2
4. lacun$.tw.
5. ((lacunar or small or subcortical or silent) adj5 (infarct$ or stroke)).tw.
6. (small vessel adj5 (stroke$ or occlusion or disease)).tw.
7. 4 or 5 or 6
8. 3 and 7
9. 9 limit 8 to human

Appendix 5 Patient information leaflet

The study is being funded by the Wellcome Trust, a medical research charity, and has been approved by the Lothian Research Ethics Committee. The results of this research will eventually be published in scientific journals read by doctors with an interest in stroke.

If you have any questions about the study, please feel free to contact our study administrator (Miss Caroline Jackson, Department of Clinical Neurosciences, Western General Hospital, Edinburgh, EH4 2XU, telephone 0131- 537 2875) who will arrange for one of the study medical staff to get in touch with you.

If you would like to speak to somebody who is not involved in this research but knows about the study, you are welcome to contact Dr Richard Davenport, Consultant Neurologist at the Western General Hospital (Department of Clinical Neurosciences, Western General Hospital, Edinburgh, EH4 2XU, telephone 0131- 537 2072).

PATIENT INFORMATION LEAFLET

INPATIENT STROKE SERVICE

You are being invited to take part in a research study. This information leaflet explains why the research is being done and what it will involve. Please take time to read it carefully and to discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw from the study at any time without having to give a reason and without it affecting your future care.

The Edinburgh Stroke Study is aiming to identify everyone who has a stroke or TIA (mini-stroke) and is referred to hospital in Edinburgh. It will provide very valuable information that will help us to find better treatments for stroke and to improve our services for patients. The study will eventually include several thousand local people.

The medical staff in this hospital will be collecting some basic information and medical details about you. This information will be kept in your medical notes as well as on a computer database, and will be kept safe and confidential. Collecting this information enables us to care for and advise you, as well as to monitor and improve our services for you and for other patients.

The doctors and other medical staff caring for you will also be arranging for some tests to help confirm the diagnosis and to find out why you may have had a stroke or TIA. This information can be helpful in choosing the best treatment for you and in reducing your risk of further strokes. The tests may include a blood test, a heart tracing (ECG), and an ultrasound scan of your heart and blood vessels as well as a brain scan.
We would like to ask your permission to use the information collected about you (along with the information about hundreds of other patients) for research purposes, to help us to address some of the many unanswered questions about the causes and consequences of strokes and TIAs.
We would also like to ask your permission to store some of the blood we take so that we can test it in the future to identify possible genetic and environmental causes of stroke which have not yet been discovered.

Any information you give us will of course be treated as confidential and will only be available to the medical staff treating you and researchers involved in this project.

To help us find out more about your illness, we would also like to ask your permission to contact your GP, to look at your medical records, and to link the information collected in this study to other NHS information on your health care held confidentially by NHS Scotland. This will give us important information about any past and future illnesses which may be related to your current problems.

We would also like to be in touch with you regularly to find out how you are getting on. This will normally involve us contacting you by post or telephone in the next few months and then every year and you filling in a questionnaire about your health. The questionnaire would only take a few minutes of your time. We may invite you to attend for a further follow-up visit (or, if you prefer, one of the study medical staff could visit you at home) so that we can make a more detailed assessment of how you are getting on. We might also contact you to invite you to participate in related research studies.

Appendix 6 Patient consent form

The Lothian University
Hospital NHS Trust
Western General Hospital

Place patient sticker here

PATIENT'S CONSENT FORM

The Edinburgh Stroke Study has been explained to me and I have read the information leaflet about it. I have had time to consider the study and have had all my questions about it answered.

	YES *(please tick)*	NO
I give my consent for the information collected about me to be used for research purposes.	☐	☐
I give my consent for my usual general practitioner to be contacted about the study, for my medical records to be examined, and for the information collected in this study to be linked to other NHS information on my health care held confidentially by NHS Scotland.	☐	☐
I give my consent for a sample of my blood to be stored so that it can be tested in the future for possible genetic and other causes of stroke which have not yet been discovered.	☐	☐
I give my consent to be contacted in the future about how I am getting on, and to be invited to attend for follow-up assessments or to participate in related research studies.	☐	☐

I understand that I am free to withdraw at any time from any part of the study, without giving a reason, and without it adversely affecting my future medical care.

Signed:……..(patient's signature)

Name:……(patient's name)

Date:……

Appendix 7 Inpatient data collection form

Lothian Stroke Care Audit / ESS Form – Clinical Inpatient Information

Address label	
Chi No.	Sex
Unit No. WG	
Name	Title
Address	

Date of admission : ____/____/____

Date of assessment : ____/____/____

Time of assessment: ____:____

Consultant in charge : _____

Final diagnosis and status (Please tick all that apply)

Cerebral[1]	Stroke (not SAH)	Transient ischaemic attack	Subarachnoid haemorrhage
Eye[1]	Retinal artery occlusion	Transient monocular blindness	
Other	Possibly cerebrovascular[2]	Details: _____	
	Definitely non-cerebrovascular	Details: _____	

Casemix assessment

Was the patient independent in ADL[3] before event ? [__] Are they oriented in time, place and person ? [__]

Was the patient living alone at the time of event ? [__] Can the patient lift both arms off the bed ? [__]

Can the patient talk[4] ? [__] Able to walk without help from another person ? [__]

NIH stroke scale score *(0-42; please complete scoring sheet on back page and see supplementary notes attached)* [_____]

Clinical assessment –presenting event(s) presenting event(s), past history & related signs

Date of onset of symptoms *(or best estimate)* ____/____/____

Time of onset of symptoms (enter ? if unknown)[5]

On aspirin at onset ? [__]

On other antiplatelet drug at onset ? [__]

On warfarin at onset? [__]

Side of brain/eye lesion *(please circle)*
Right / Left / Cerebellar or brainstem / Bilateral / Uncertain

Blood pressure at time of assessment [_____/_____]

Height (cm) [_____] *or* half - armspan[5] (cm) [_____]

Weight (to nearest kg) [_____]

Prior stroke (before presenting event(s)) ?[__]

Prior TIA (before presenting event(s)) ? [__]

History of ischaemic heart disease[6] ? [__]

History of treated hypertension ? [__]

History of diabetes mellitus ? [__]

Peripheral arterial disease[7] ? [__]

Cardiac failure[8] ? [__]

Clear history of atrial fibrillation ? [__]
(paroxysmal or persistent)

[1] Use these categories for **definite** or **probable** (>50% certain) cerebrovascular diagnoses
[2] Use if presentation could have cerebrovascular cause but < 50% certain and give details (e.g. lone vertigo)
[3] Independent in **walking, dressing, washing, feeding,** and **toileting**, not necessarily bathing, shopping or climbing stairs
[4] Able to utter understandable words even if quiet or slurred
[5] Mid-sternal notch to tip of middle finger with (non-paretic) arm outstretched at right angles to body and palm facing forward
[6] MI (including ECG evidence of silent MI) / angina /CABG/coronary angioplasty or stent etc.
[7] History of claudication / rest pain / peripheral arterial intervention, or definite signs (absent foot pulses / femoral arterial bruit)
[8] Definite clinical signs of heart failure or taking at least two drugs for its treatment (eg. ACE-inhibitor and loop diuretic)

Codes for boxes [__]:			
	Yes	Y	Wider boxes are for **numbers**
	No	N	Please use ? for unknown
	Unknown	?	**Dates**: please use ?? for unknown, and
	Unassessable	=	complete what you can (e.g. ??/12/1980)

Clinical assessment - social and family history

Cigarette smoker ? *(please circle)* : Never / Ex>12 m / Current or ex<12 m / Unknown

If current or ex <12 m cigarette smoker, cigarettes / day ? [_____]

Alcohol intake (units/week) [_____]

1st degree relative with stroke / TIA ? [__] Mother / Father / Sibling(s) / Child(ren)
(please circle all that apply) :

If yes, how many 1st degree relatives in total? *(please circle)* : 1 / 2 / >2

1st degree relative with IHD / PAD[9] ? [__] Mother / Father / Sibling(s) / Child(ren)
(please circle all that apply):

If yes, how many 1st degree relatives in total? *(please circle)* : 1 / 2 / >2

Edinburgh Stroke Study information / consent
*(if full consent already available following a previous event, simply write **"CONSENT OBTAINED ALREADY"** across this box)*
Patient / relatives given info pack with consent form? [__]

Consent for ESS: Patient / Relative / Witnessed / Waiver / Refused / None yet
(please circle- see patient information sheet and consent forms for details)
Consent date: ____/____/____

Use of data for research purposes [__] Blood for research [__]

Contact GP / examine medical records [__] Follow-up [__]

Clinical classification of stroke / TIA syndrome[10] LACS / PACS / POCS / TACS / Eye[11] / Uncertain
(please circle):

Other risk factors or unusual cause of stroke or TIA ? [__] (circle any options that apply and give details)

coronary catheterisation / carotid endarterectomy / cardiac valve disease / haematological illness /

hereditary e.g. CADASIL / arterial dissection / coagulopathy / other

Details : _____

Clinical prediction of dependency at six months *(clinician's 'gut feeling' : 0-6 on Oxford Handicap scale[12])*
[_____]

Assessing clinician *(please circle)*

MSD / RIL / PAGS / CPW / CLMS / BW / VC / Other *(please initial)* : _____

[9] ischaemic heart disease / peripheral arterial disease
[10] Based on clinical assessment *before* results of imaging or other investigations
[11] Use for transient monocular blindness / retinal artery occlusion
[12] Oxford Handicap Scale:
0 = no symptoms;
1 = minor symptoms which do not interfere with lifestyle;
2 = some restriction to lifestyle but look after themselves;
3 = significant restriction to lifestyle, preventing total independence;
4 = severe handicap preventing independent existence but not requiring constant attention;
5 = severe handicap, totally dependent, requiring attention night and day
6 = dead

Admission blood tests	Taken ? *(please tick)*	Date taken:	Result *(leave blank if not yet known)*	
FBC	☐	____/____/____	Haemoglobin (g/l)	[_____]
			Haematocrit (ratio)	[0●_____]
			White cell count (x10^9/l)	[____●___]
			Platelets (x10^9/l)	[_____]
ESR	☐	____/____/____	(mm/hour)	[_____]
U&E	☐	____/____/____	Urea (mmol/l)	[____●___]
			Creatinine (µmol/l)	[_____]
Glucose	☐	____/____/____	(mmol/l)	[____●___]
Lipids	☐	____/____/____	Total cholesterol (mmol/l)	[____●___]
			HDL cholesterol (mmol/l)	[____●___]
Research	☐	____/____/____		

Brain imaging and final classification

CT done ? [__] Date : ____/____/____ Evidence of new haemorrhage on CT/MRI[13] ?[__]

MRI done ? [__] Date : ____/____/____ Visible relevant infarct on CT/MRI ? [__]

Final syndrome classification :
(using all clinical and imaging information) LACS / PACS / POCS / TACS / Uncertain / Eye[14]

Cardiac investigations

ECG since event available ? [__] AF on ECG ? [__]
LVH on ECG[15] ? [__]

Echocardiogram done?*(please circle):* None / TTE no contrast / TTE+contrast / TOE no contrast / TOE+contrast
Date of first echocardiogram : ____/____/____ LVH on echo ? [__]

Carotid imaging
Carotid Duplex examination performed ? [__] Date of 1st Duplex ____/____/____
2nd Carotid Duplex performed ? [__] Date of 2nd Duplex ____/____/____
MR Angiography performed ? [__] Date of MRA ____/____/____
CT Angiography performed ? [__] Date of CTA ____/____/____
Conventional Angiography performed ? [__] Date of angiography ____/____/____

Carotid imaging results	Right	Left
ICA % stenosis on Duplex[16] ?	[_____]	[_____]
Post-stenotic collapse (equivalent on Duplex) ?	[__]	[__]
Plaque instability / irregularity (on Duplex or MRA) ?	[__]	[__]

Codes for boxes [__]:			
	Yes	Y	Wider boxes are for **numbers**
	No	N	Please use ? for unknown
	Unknown	?	**Dates**: please use ?? for unknown, and
	Unassessable	=	complete what you can (e.g. ??/12/1980)

[13] Include harmorrhagic transformation of infarct but **NOT** petechial haemorrhage / microbleeds
[14] Use for transient monocular blindness / retinal artery occlusion
[15] **Don't rely on automatic report.** Use voltage criteria – sum of S wave in V_1 or V_2 + R wave in V_5 or $V_6 \geq 3.5$ mV (35 mm)
[16] Record discrete figure or range. If >1 result, record most severe. If result 'normal' record 0%; if 'minor atheroma' record 30%.

NIH Stroke Scale (Please circle the most appropriate response for each section. See supplementary notes attached. If untestable please state reason. Add the scores for each item to get the total, and do not count untestable items)

1a Level of Consciousness (LOC)	0 1 2 3	Alert – *keenly responsive* Drowsy – *arousable by minor stimulation to obey, answer, or respond* Stuporous – *requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped*) Comatose – *responds only with reflex motor or autonomic effects or totally unresponsive*
1b LOC Questions	0 1 2	Answers both correctly Answers one correctly Incorrect Patient is asked to state the month & his/her age. No credit for partly correct answers.
1c LOC Commands	0 1 2	Obeys both correctly Obeys one correctly Incorrect Patient is asked to close & open eyes, grip & release normal hand
2. Best Gaze	0 1 2	Normal Partial gaze palsy – *gaze is abnormal in one or both eyes, no forced deviation/total gaze paresis* Forced deviation – *or total gaze paresis not overcome by oculocephalic maneouvre*
3. Visual Fields	0 1 2 3	No visual loss Partial hemianopia or visual inattention Complete hemianopia Bilateral hemianopia – *including cortical blindness*
4. Facial Palsy	0 1 2 3	Normal Minor - *flattened nasolabial fold, asymmetry on smiling* Partial – *total or near total paralysis of lower face* Complete - *absent facial movement in upper and lower face on one or both sides*
5. Best Motor RIGHT ARM	0 1 2 3 4 x	No drift – *holds limb at 90 degrees for full 10 seconds* Drift - *drifts down but does not hit bed* Some effort against gravity No effort against gravity No movement *Untestable (only for amputation or shoulder joint fusion – please state which)*
6. Best Motor LEFT ARM	0 1 2 3 4 x	No drift – *holds limb at 90 degrees for full 10 seconds* Drift - *drifts down but does not hit bed* Some effort against gravity No effort against gravity No movement *Untestable (only for amputation or shoulder joint fusion – please state which)*
7. Best Motor RIGHT LEG	0 1 2 3 4 x	No drift – *holds limb at 45 degrees for full 5 seconds* Drift - *drifts down but does not hit bed* Some effort against gravity No effort against gravity No movement *Untestable (only for amputation or hip joint fusion – please state which)*
8. Best Motor LEFT LEG	0 1 2 3 4 x	No drift – *holds limb at 45 degrees for full 5 seconds* Drift - *drifts down but does not hit bed* Some effort against gravity No effort against gravity No movement *Untestable (only for amputation or hip joint fusion – please state which)*
9. Limb Ataxia	0 1 2 x	Absent Present in 1 limb Present in 2 or more limbs *Untestable (only for amputation or joint fusion – please state which)*
10. Sensory	0 1 2	Normal Partial loss - *patient feels pinprick is less sharp or is dull on affected side* Dense loss - *patient is unaware of being touched on face, arm, leg*
11. Best Language	0 1 2 3	No dysphasia Mild to moderate dysphasia - *obvious loss of fluency or comprehension, without significant limitation in ideas expressed or form of expression. Conversation about provided material difficult or impossible but examiner can identify items from patient's response.* Severe dysphasia - *all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener who carries burden of communication. Examiner cannot identify items provided from patient response.* Mute - *no usable speech or auditory comprehension.*
12. Dysarthria	0 1 2 x	Normal articulation Mild to moderate dysarthria - *patient slurs some words, can be understood with some difficulty.* Unintelligible or worse - *speech is so slurred as to be unintelligible (absence of or out of proportion to dysphasia) or is mute/anarthric* *Untestable (intubation or other physical barrier to producing speech – please state)*
13. Neglect	0 1 2	No neglect Partial neglect - *Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities* Complete neglect - *Profound hemi-inattention (e.g. does not recognise own hand or orients to only one side of space) or hemi-inattention to more than one sensary modality (e.g. visual + tactile).*

Codes for boxes [__]:	Yes	Y	Wider boxes are for **numbers**
	No	N	Please use ? for unknown
	Unknown	?	**Dates**: please use ?? for unknown, and
	Unassessable	=	complete what you can (e.g. ??/12/1980)

Appendix 8 Outpatient data collection form

LOTHIAN STROKE CARE AUDIT / REGISTRATION FORM – Outpatients

Address label

Chi No. Sex

Unit No. WG

Name Title

GP Initials_____ GP Surname_____

GP Postcode _____ GP Phone _____

Date of assessment ____/____/____

Responsible consultant _____ Unit : WGH

Date of referral ____/____/____ From GP ? [__]

Date referral received ____/____/____

Date of first appointment offered ____/____/____

Final diagnosis (of presenting event(s)) (Please tick all that apply)

Cerebral[1]	Stroke (not SAH) ☐	Transient ischaemic attack ☐	Subarachnoid haemorrhage ☐
Eye[1]	Retinal artery occlusion ☐	Transient monocular blindness ☐	
Other	Possibly cerebrovascular[2] ☐	Details: _____	
	Definitely non-cerebrovascular ☐	Details: _____	

Complete remainder of form only if definite / probable cerebrovascular diagnosis within last 6 months

Casemix assessment (complete for STROKE PATIENTS ONLY - refers to most recent event)

Was the patient independent in ADL[3] before event ? [__] Are they oriented in time, place and person ? [__]

Was the patient living alone at the time of event ? [__] Can the patient lift both arms off the bed ? [__]

Can the patient talk[4] ? [__] Able to walk without help from another person ? [__]

NIH stroke scale score *(0-42; please complete attached scoring sheet)* [_____]

Clinical assessment – presenting event(s), past history & related signs

Date of most recent stroke / TIA / eye attack ____/____/____ *(or best estimate)*

Prior stroke - before presenting event(s) ? [__]

Number of TIAs (not strokes) in the last 3 months [_____]

Prior TIA - before presenting event(s) ? [__]

Any stroke symptoms lasting > 7 days[5] ? [__]

History of ischaemic heart disease[6] ? [__]

Side of brain/eye lesion *(please circle)*
Right / Left / Cerebellar or brainstem / Bilateral / Uncertain

History of treated hypertension ? [__]

Have there been carotid *and* vertebral events ? [__]

History of diabetes mellitus ? [__]

Residual neurological signs from presenting event(s) ? [__]

Peripheral arterial disease[7] ? [__]

Any symptomatic neck bruit ? [__]

Cardiac failure[8] ? [__]

Blood pressure [_____/_____]

Clear history of atrial fibrillation ? [__]

Height (cm) [_____]

Weight (to nearest kg) [_____]

Clinical assessment - social and family history

---

[1] Use these categories for **definite** or **probable** (>50% probability) cerebrovascular diagnoses within last 6 months

[2] Use and give details: if < 50% probability cerebrovascular cause (e.g. lone vertigo); or if presenting event(s) not within last 6/12

[3] Independent in **walking, dressing, washing, feeding,** and **toileting**, not necessarily bathing, shopping or climbing stairs

[4] Able to utter understandable words even if quiet or slurred

[5] Only count focal neurological symptoms. If too soon to be sure, please code as unassessable

[6] MI (including ECG evidence of silent MI) / angina /CABG/coronary angioplasty or stent etc.

[7] History of claudication / rest pain / peripheral arterial intervention, or definite signs (absent foot pulses / femoral arterial bruit)

[8] Definite clinical signs of heart failure or taking at least two drugs for its treatment (eg. ACE-inhibitor and loop diuretic)

Cigarette smoker ? *(please circle)* : Never / Ex>12 m / Current or ex<12 m / Pipe or cigars only / Unknown	
If current or ex <12 m cigarette smoker,	cigarettes / day ? [_____]
Alcohol intake	(units/week) [_____]
1st degree relative with stroke / TIA ? [__] *(please circle all that apply)* :	Mother / Father / Sibling(s) / Child(ren)
If yes, how many ? *(please circle)* :	1 / 2 / >2
1st degree relative with IHD / PAD[9] ? [__] *(please circle all that apply)*:	Mother / Father / Sibling(s) / Child(ren)
If yes, how many ? *(please circle)* :	1 / 2 / >2

Data to audit use of 2^{ary} preventative drugs
(for each column, please tick all that apply or confirm NONE at foot)

Use of following drugs :	At time of event for which referred	At time of first assessment	Recommended following NV assessment	**But** record if patient known not to tolerate
Aspirin	☐	☐	☐	☐
Dipyridamole (Persantin/Asasantin)	☐	☐	☐	☐
Clopidogrel (Plavix)	☐	☐	☐	☐
Warfarin	☐	☐	☐	☐
ACE inhibitor	☐	☐	☐	☐
Diuretic	☐	☐	☐	☐
Other antihypertensive	☐	☐	☐	☐
Statin / lipid lowering agent	☐	☐	☐	☐
NONE	☐	☐	☐	n/a

Edinburgh Stroke Study consent

*(if full consent already available following a previous event, simply write **"CONSENT OBTAINED ALREADY"** across this box)*

Consent obtained for ESS ? *(please circle - see patient information sheet and consent forms for details)*	Patient / Relative / Witnessed / None
	Consent date : ____/____/____
Use of data for research purposes [__]	Blood for research [__]
Contact GP / examine medical records [__]	Follow-up [__]

Codes for boxes [__]:	Yes	Y	Wider boxes are for **numbers**
	No	N	Please use ? for unknown
	Unknown	?	**Dates**: please use ?? for unknown, and complete what
	Unassessable	=	you can (e.g. ??/12/1980)

[9] ischaemic heart disease / peripheral arterial disease

Blood tests	Done prior to clinic	Taken in clinic	Date blood taken:	Result *(leave blank if not yet known)*	
FBC	☐	☐	____/____/___	Haemoglobin (g/l)	[_____]
				Haematocrit (ratio)	[0●_____]
				White cell count (x10^9/l)	[____●___]
				Platelets (x10^9/l)	[_____]
ESR	☐	☐	____/____/___	(mm/hour)	[_____]
U&E	☐	☐	____/____/___	Urea (mmol/l) [____●___]	
				Creatinine (μmol/l)	[_____]
Glucose	☐	☐	____/____/___	(mmol/l)	[____●___]
Lipids	☐	☐	____/____/___	Total cholesterol (mmol/l)	[____●___]
				HDL cholesterol (mmol/l)	[____●___]
Research[10]		☐	____/____/___		
NONE[11]	☐				

Clinical classification
of presenting stroke / TIA syndrome[12] *(please circle)* LACS / PACS / POCS / TACS / Eye[13] / Uncertain

Other risk factors or unusual cause of stroke or TIA ? **[__]** (circle any options that apply and give details)
coronary catheterisation / carotid endarterectomy / cardiac valve disease / haematological illness / hereditary e.g. CADASIL / arterial dissection / coagulopathy / other
Details : _____

Clinical prediction of outcome *(clinician's 'gut feeling')*

Probability of stroke (%)	at one year	[_____]	at five years	[_____]
Probability of vascular event (%) *(stroke, MI or vascular death)*	at one year	[_____]	at five years	[_____]
Dependency *(for **STROKE PATIENTS ONLY**)* *(0-6 on Oxford Handicap scale[14])*	at six months	[_____]		
Assessing clinician *(please circle)*	MSD / RIL / PAGS / CPW / CLMS / BW / Other *(please initial)* : _____			

[10] For research bloods, please fill completely: two normal 2.7 ml EDTA tubes (red top). Label with hospital patient stickies. Research samples should be kept in the ice box provided and will be sent to the Wellcome Trust Clinical Research Facility at the end of the clinic.
[11] Tick this box if no blood tests done since referral event(s)
[12] Based on clinical assessment *before* results of imaging / other tests. If patient presents with TIA *and* stroke, classify the stroke.
[13] Use for transient monocular blindness / retinal artery occlusion
[14] Oxford Handicap Scale:
0 = no symptoms;
1 = minor symptoms which do not interfere with lifestyle;
2 = some restriction to lifestyle but look after themselves;
3 = significant restriction to lifestyle, preventing total independence;
4 = severe handicap preventing independent existence but not requiring constant attention;
5 = severe handicap, totally dependent, requiring attention night and day
6 = dead

Codes for boxes [__]:			
	Yes	Y	Wider boxes are for **numbers**
	No	N	Please use ? for unknown
	Unknown	?	**Dates**: please use ?? for unknown, and
	Unassessable	=	complete what you can (e.g. ??/12/1980)

Cardiac investigations

ECG since event available ? [__]

AF on ECG ? [__]

LVH on ECG ? [__]

Echocardiogram done ?*(please circle):* None / TTE no contrast / TTE+contrast / TOE no contrast / TOE+contrast

Date of first echocardiogram : ____/____/____

Patent foramen ovale on echo? [__]

LVH on echo ? [__]

Data to audit carotid intervention service

Carotid Duplex examination performed ?	[__]	Date of 1st Duplex	____/____/____
2nd Carotid Duplex performed ?	[__]	Date of 2nd Duplex	____/____/____
MR Angiography performed ?	[__]	Date of MRA	____/____/____
CT Angiography performed ?	[__]	Date of CTA	____/____/____
Conventional Angiography performed ?	[__]	Date of angiography	____/____/____
Referred to vascular surgeons/interventional radiologist ?	[__]	Date referred	____/____/____

If not referred, why ? (please circle reason): patient choice / clinically not worthwhile (doctors decision) / mutual agreement / not appropriate (no severe stenosis)

If referred – intervention considered *(please circle)*: surgery / angioplasty ± stent

Seen by surgeon / radiologist ?	[__]	Date seen	____/____/____
Intervention performed ?	[__]		
If yes Side *(please circle)* Right / Left / Both		Date of (first) procedure	____/____/____
Stroke within 30 days of intervention ?	[__]		
Other complication(s) of intervention ?	[__]	*(please specify)*	_____
Reviewed in NV clinic after intervention ?	[__]	Date reviewed	____/____/____

Carotid imaging results	*Right*	*Left*
ICA % stenosis on 1st Duplex[15] ?	[_____]	[_____]
Post-stenotic collapse (equivalent on Duplex) ?	[__]	[__]
Plaque instability / irregularity (on Duplex or MRA) ?	[__]	[__]

[14] Include harmorrhagic transformation of infarct but **NOT** petechial haemorrhage / microbleeds

[15] Use for transient monocular blindness / retinal artery occlusion

[16] **Don't rely on automatic report.** Use voltage criteria – sum of S wave in V_1 or V_2 + R wave in V_5 or $V_6 \geq 3.5$ mV (35 mm)

[17] Record discrete figure or range. If >1 result, record most severe. If result 'normal' record 0%; if 'minor atheroma' record 30%.

Codes for boxes [__]:	Yes	Y	Wider boxes are for **numbers**
	No	N	Please use ? for unknown
	Unknown	?	**Dates**: please use ?? for unknown, and
	Unassessable	=	complete what you can (e.g. ??/12/1980)

Appendix 9 Follow-up questionnaire

FOLLOW-UP QUESTIONNAIRE

CONFIDENTIAL

«TITL» «INIT» «SURNAME»
«ADDRESS_1»
«ADDRESS_2»
«ADDRESS_3»

«Date»

Department of Clinical Neurosciences
University of Edinburgh
Bramwell Dott Building
Western General Hospital
Crewe Road
Edinburgh
EH4 2XU
Tel: 0131 537 2875
Fax: 0131 332 5150
E-mail: ess@skull.dcn.ed.ac.uk
Web: www.dcn.ed.ac.uk/ess

Dear «TITL» «SURNAME»

You were seen at the Western General Hospital on «EXAM_D» and we would now be very interested to find out how you are getting on.

We would be grateful if you or someone who knows you well could complete and return the questionnaire in the envelope enclosed. No stamp is required. Should you have any problems completing the questionnaire, please do not hesitate to contact Miss Caroline Jackson on 0131 537 2875.
All information received will be kept strictly confidential.

Many thanks for your help

Yours sincerely

Dr Martin Dennis
Consultant Physician

Dr Cathie Sudlow
Specialist Registrar in Neurology

	YES	NO
	(Please tick one box)	
1. **Has the stroke left you with any problems?**	☐	☐

	YES	NO
	(Please tick one box)	
2. **Do you need help from anybody with everyday activities?**	☐	☐

	YES	NO
3. How do you live now?	*(Please tick one box)*	
On my own	☐	☐
With my partner or relatives	☐	☐

	YES	NO
4. Where do you live now?	*(Please tick one box)*	
In my own home or my relative's home	☐	☐
In a residential home	☐	☐
In a nursing home	☐	☐

	YES	NO
5. **Have you had any FURTHER weakness or numbness in your legs or arms or have you had any NEW problems with your vision or speech since «LAST_SEEN»?** (*Please tick one box)*	☐	☐
If **YES,** did you attend your GP or hospital?	☐	☐

Date attended: ……../……./……..

	YES	NO
6. **Has a doctor told you that you have had a stroke or 'shock' since «LAST_SEEN»**? *(Please tick one box)*	☐	☐

If **YES**, who told you?……

When? (approximately) Date: ……../……../……..

	YES	NO
7. **Have you had any chest pains since «LAST_SEEN»?** *(Please tick one box)*	☐	☐
If **YES**, did you attend your GP or hospital?		

Date attended: ……/……/……

	YES	NO
8. **Has any doctor told you that you have had a heart attack since «LAST_SEEN»?** *(Please tick one box)*	☐	☐

If **YES**, who told you?……

When? (approximately) Date: ……../……../……..

9. **Tick the ONE box next to the sentence which best describes your present state.**

I have no symptoms at all.	☐
I have a few symptoms but these do not interfere with my everyday life**.**	☐
I have symptoms which have caused some changes in my life but I am still able to look after myself.	☐
I have symptoms which have significantly changed my life and I need some help in looking after myself.	☐
I have quite severe symptoms which mean I need to have help from other people but I am not as bad as to need attention day and night.	☐
I have major symptoms which handicap me and I need constant attention day and night.	☐

Please note the date you completed this form: ……../……../……..

Thank you for completing the questionnaire. Please now return it in the pre-paid envelope enclosed.

Appendix 10 (a) Study contact card given to patients and (b) Study sticker provided to General Practitioners and placed on the front of hospital medical records

(a)

Front:

Thank you for joining the Edinburgh Stroke Study

How to contact us:
Telephone: 0131 5372875

Fax: 0131 332 5150
E-mail: ess@skull.dcn.ed.ac.uk

Edinburgh Stroke Study, Dept of Clinical Neurosciences, Bramwell Dott Building, Western General Hospital, Edinburgh EH4 2XU

Back:

If, at any time in the future, you have:

- **new** weakness or numbness in your legs or arms; *or*
- **new** problems with vision or speech

you **might** have had another stroke. You should:

- seek medical help straight away
- please let the Edinburgh Stroke Study know as soon as possible.

(b)

Please let us know as soon as possible if this patient may have had a further stroke or a MI. **Dr Cathie Sudlow / Dr Martin Dennis** **Department of Clinical Neurosciences** **Western General Hospital** **Tel: 0131 537 2875** **Fax: 0131 332 5150** **E-mail: ess@skull.dcn.ed.ac.uk** **Web: www.dcn.ed.ac.uk/ess**	**This Patient is enrolled in the Edinburgh Stroke Study**

Appendix 11 General Practitioner outcome event survey form

«FORENAME» «Second_name»
Date of birth: «DOB»
«ADDR_1» «ADDR_2» «ADDR_3»

If the patient is no longer registered at your practice, please tick this box. ☐
You do not need to complete the rest of the form. Please return the form to us using the enclosed freepost envelope.

1. As far as you know, has the patient had any further strokes **since they were seen** by the stroke team at the Western General Hospital on *insert date of assessment* ?

Yes ☐ If Yes, how many strokes? ___ No ☐ If No, go to question 2

Date(s) of further stroke(s): 1: __/__/____ 2: __/__/____ 3: __/__/____

Was the patient ever admitted to hospital with a further stroke? Yes ☐ No ☐

If yes, which hospital? (please tick all that apply)

Royal Infirmary of Edinburgh ☐

Western General Hospital ☐

Other (please give details) _____

2. As far as you know, has the patient had a myocardial infarction (MI) **since they were seen** by the stroke team at the Western General Hospital on *insert date of assessment*?

Yes ☐ If Yes, how many MIs ? ___ No ☐ If No, form now complete for return

Date(s) of MI(s) 1: __/__/____ 2: __/__/____ 3: __/__/____

Was the patient ever admitted to hospital with a MI? Yes ☐ No ☐

If yes, which hospital? (please tick all that apply)

Royal Infirmary of Edinburgh ☐

Western General Hospital ☐

Other (please give details) _____

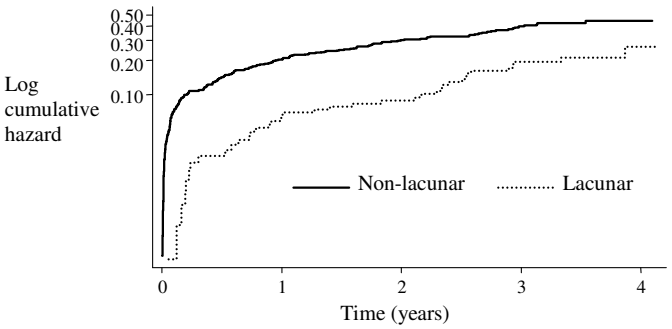
Thank you very much for taking the time to complete the form. If you have any questions, please contact Caroline Jackson (tel: 0131 - 537 2875, email: caroline.jackson@ed.ac.uk).

Please return the form to us using the freepost envelope enclosed.

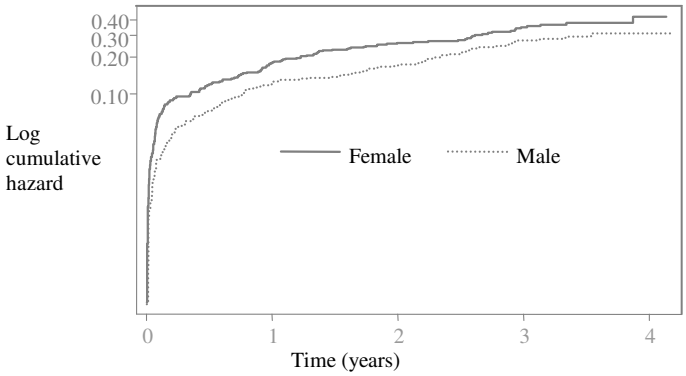
(Edinburgh Stroke Study, Division of Clinical Neurosciences, Bramwell Dott Building, Western General Hospital, Edinburgh, EH4 2XU)

Appendix 12 (a) Assessment of the proportional hazards assumption for variables included in the Cox regression model comparing risk of death in lacunar versus non-lacunar patients

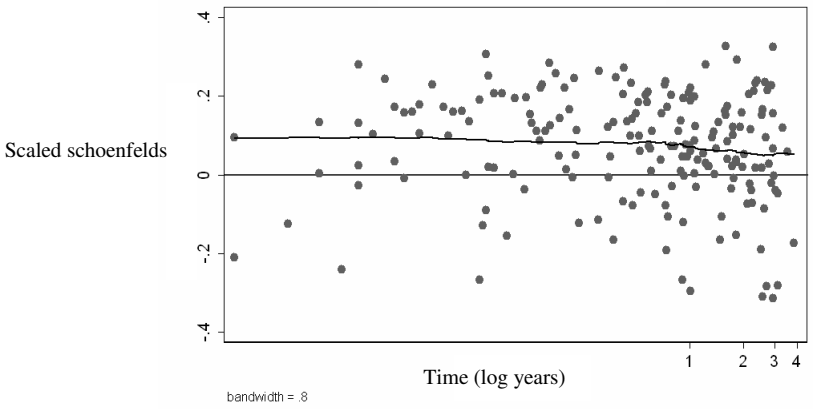
(i) stroke subtype



(ii) gender

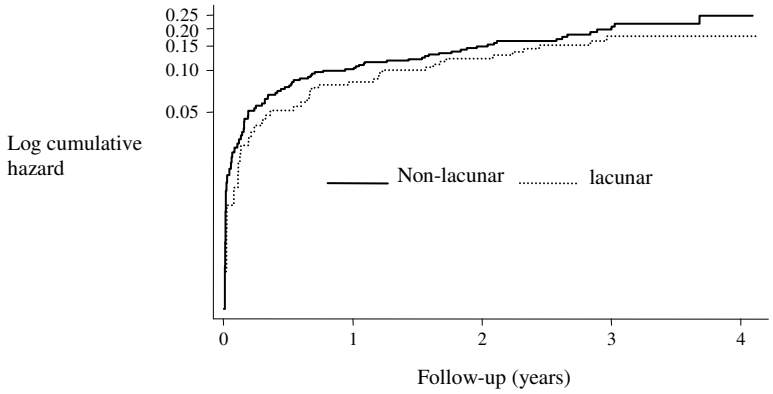


(iii) Age

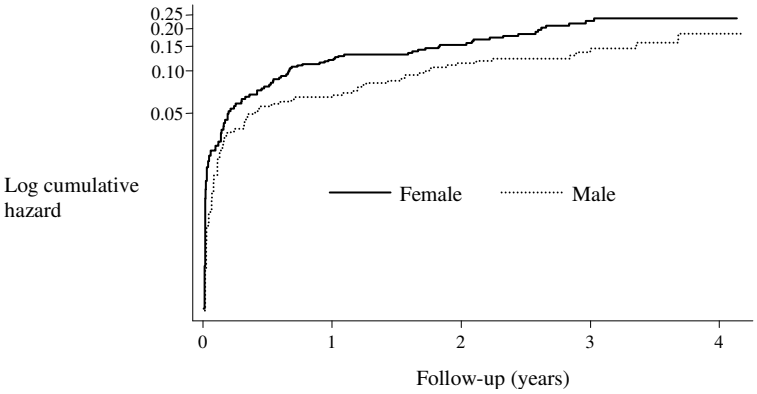


Appendix 12 (b) Assessment of the proportional hazards assumption for variables included in the Cox regression model comparing risk of recurrent stroke in lacunar versus non-lacunar patients

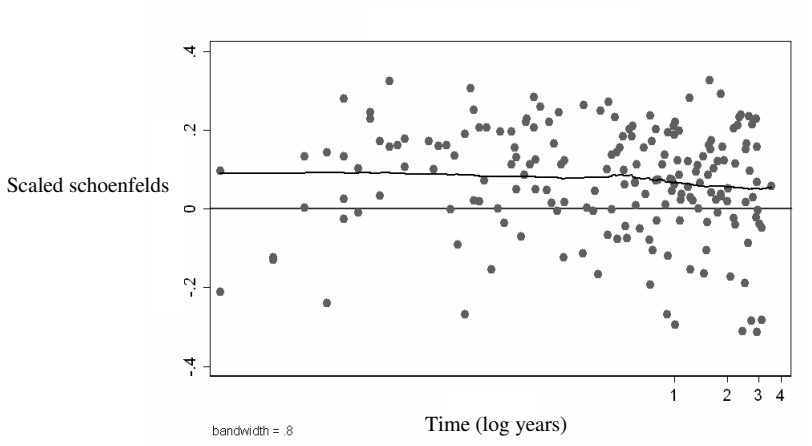
(i) Stroke subtype



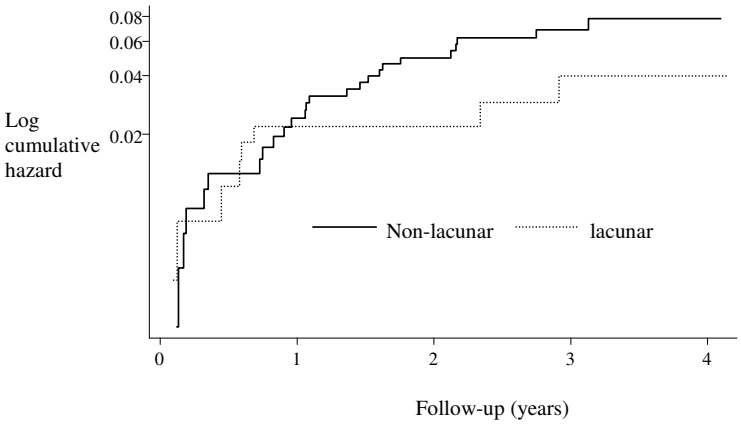
(ii) Gender



(iii) Age



Appendix 12 (c) Assessment of the proportional hazards assumption for risk of myocardial infarction, comparing lacunar with non-lacunar ischaemic stroke



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